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Abstracts

Invited Speakers

1
DOES SERONEGATIVE APS REALLY EXIST? - CONS

R. Cervera
Autoimmune Diseases, Hospital Clínic, Barcelona, Spain

Many studies since the early 80's have found that patients with antiphospholipid antibodies (aPL) are prone to repeated episodes of venous or arterial thrombosis, recurrent fetal losses, and thrombocytopenia, among other manifestations. The term antiphospholipid syndrome (APS) was introduced as a means of classifying those patients with aPL and the above mentioned clinical events. More recently, some patients with the clinical manifestations of this syndrome but with negativity of aPL in the usual routine determinations have been described. Some authors have called this phenomenon "seronegative" APS. In our opinion, the existence of clinical manifestations suggesting a diagnosis of APS requires a careful and repeated search for aPL. A work-up is needed before a patient should be considered as having "seronegative" APS, including repeat aPL testing at some reasonable time point after the thrombotic event (probably this time can be as long as 6-7 months afterwards) to rule out aPL consumption during the course of the thrombotic event.

2
IS FIBROMYALGIA ALL IN YOUR MIND?

B. Van Houdenhove
Psychiatry, K.U. Leuven, Leuven, Belgium

In this presentation, I will present recent evidence on the following topics: 1) Fibromyalgia (FM) largely overlaps with other functional somatic syndromes, and particularly chronic fatigue syndrome (CFS); 2) Retrospective and prospective studies suggest that physical and/or psychosocial stressors may play an important etiological role in both FM and CFS; 3) Modern neurobiological stress research increasingly shows how stress via neural, neuroendocinological and immunological pathways may substantially contribute to central sensitization and effort intolerance, two key-features of both FM and CFS.

3
THROMBOPROPHYLAXIS IN APL CARRIERS WITHOUT PREVIOUS THROMBOSIS - CONS

G. Finazzi
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Thromboprophylaxis with aspirin is not indicated in all asymptomatic patients with confirmed aPL positivity because: a) the estimated prevalence of thrombosis in unselected cases is about 1% patient-years (range 0-2.8); b) this level of thrombotic risk is equivalent to that of major bleeding associated with the use of aspirin and therefore the expected benefit does not outweigh the risk; c) these expectations have been confirmed by at least one randomized clinical trial, although with methodological limits (Erkan *et al*. *Arthritis Rheum* 2007; 56: 2382-91). The management of modifiable thrombotic risk factors can be an alternative and safer strategy, considering that many vascular events occur in the presence of concomitant non-aPL triggering conditions. Whether primary prophylaxis with aspirin may be useful for some subsets of aPL patients at particularly high thrombotic risk, such as those with overt SLE or with special patterns of antibodies, remains to be established in appropriate clinical studies.

4
PATIENTS WITH AUTO-IMMUNE INFLAMMATORY RHEUMATIC DISEASES (AIIRD) SHOULD RECEIVE VACCINATIONS TO PREVENT INFECTIOUS DISEASES AS RECOMMENDED BY EULAR

M. Bijl
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The introduction of vaccinations against has been a major break-through in the battle against bacterial and viral microorganisms. Morbidity and mortality due to many vaccine-preventable diseases have been successfully reduced.

Patients with auto-immune inflammatory rheumatic diseases (AIIRD) are at increased risk of contracting infections due to the underlying disease as well as the immunosuppressive treatment they often receive to reduce or prevent disease activity. Infectious diseases are one of the leading causes of morbidity and even mortality in AIIRD patients. Many of these infections might be prevented by vaccination. The efficacy of vaccinations, however, may be reduced in patients with AIIRD. Moreover, safety of vaccination in patients with AIIRD is an important issue, because of a potential risk of flares of the underlying AIIRD following vaccination.
Recently, recommendations for vaccination in patients with AIIRD the European League Against Rheumatism (EULAR) have been published (1), developed by evidence-based and expert opinion-based approaches (2). Although some concerns about safety still exist the net effect of vaccination in these patients is favourable: most vaccines are effective and side effects are mild. During the session the arguments in favour of vaccination will be highlighted.

References:

1. VAN ASSEN S, *et al*.: EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2010.
2. VAN ASSEN S, *et al*.: Vaccination in adult patients with auto-immune inflammatory rheumatic diseases: systematic literature review for the EULAR evidence-based recommendations for vaccination. *Autoimmun Rev* 2010.

5
'ASIA'-AUTOIMMUNE (AUTO-INFLAMMATORY) SYNDROMES INDUCED BY ADJUVANTS

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In the last decades four enigmatic medical conditions were described, all of which were characterized by an hyperactive immune response as well as similar clinical and laboratory manifestations. These conditions, namely siliconosis, the Gulf war syndrome (GWS), the macrophagic myofasciitis syndrome (MMF) and post vaccination phenomena represent environmental factors that may play a role in inducing or aggravating autoimmunity and auto-inflammation.
In rare occasions vaccines may induce autoimmune or auto-inflammatory conditions both in animals and in humans (1). The susceptibility factors and the temporal association between vaccines and these rare immune mediated reactions are yet to be defined, however the similarities between vaccines and infections and the addition of an adjuvant (i.e.alum, squalene, etc.) to almost every vaccine are considered major contributors to such adverse events.
Another immune mediated phenomena leading to autoimmune diseases is exposure to silicone (i.e.breast implant).
A common denominator to each syndrome as well as to various infectious agents is the trigger entailing adjuvant activity (2).
Thus, herein we would like to suggest to include these four conditions under a common syndrome entitled the "Autoimmune (Auto-inflammatory) Syndrome induced by adjuvants" (ASIA) (3). We propose several major and minor criteria that may aid in the diagnosis of this newly defined condition(ASIA).

References:

1. AGMON-LEVIN N, PAZ Z, ISRAELI E, SHOENFELD Y: Vaccines and autoimminty. *Nat Rev Rheumatol* 2009; 5: 648-52.
2. ISRAELI E, AGMON-LEVIN N, BLANK M, SHOENFELD Y: Adjuvants and autoimmunity. *Lupus* 2009;18:1217-1225.
3. SHOENFELD Y, AGMON-LEVIN N: 'ASIA' - autoimmune / inflammatory syndrome induced by adjuvants. *J of Autoimmun* 2010, In press.

6
TARGETING AUTOREACTIVE B CELLS IN SLE: THE ROLE OF BLYS

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BLyS (also known as BAFF, B- cell activating factor) is a member of the TNF ligand superfamily, it is produced by macrophages, dendritic cells and neutrophils, and binds to three different receptors expressed on B cells and plasma cells. BLyS appears to have limited or no effects on B-lymphocyte precursors (pre-B cells in the bone marrow), which do not express any of the known BLyS receptors. Its biologically active form can enhance B lymphocyte activation and prolong B lymphocyte survival.
In mice elevated levels of BLyS are associated with lymphoid hyperplasia and features of autoimmunity (autoantibody production, and SLE or Sjögren's like diseases). In animal models treatment with BLyS antagonists is able to reduce disease progression and to increase survival.

Evidence of increased circulating BLyS levels in patients with autoimmune diseases, such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), rheumatoid arthritis (RA) and scleroderma, has also been reported.
In patients with SLE, BlyS is overexpressed and a correlation between BlyS levels and disease activity has been described. More specifically plasma levels of BlyS were associated with anti-dsDNA antibodies titers and with disease activity as measured with the SELENA-SLEDAI index. In addition a correlation has been described between elevated BLyS level at the previous visit and a greater SELENA-SLEDAI score at the subsequent evaluation.
These animal and human data, have supported the hypothesis that BLyS could represent a target for new SLE treatment.

7
PREDICTIVE FACTORS FOR RITUXIMAB RESPONSE IN RHEUMATOID ARTHRTIS

A. Finckh
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B-cell depletion with Rituximab (RTX) has proved to be effective in treating moderate to severe rheumatoid arthritis (RA). But, as for all biologic antirheumatic agents, RTX does not work for all patients and approximately a quarter of patients do not respond adequately to this agent. Heterogeneous responses to therapy and our relative inability to predict individual responses to specific therapies make the choice of therapy difficult. For individual patients, rheumatologist need to balance the promises of therapeutic benefit against the risk of drug associated harm. Currently, the choice of an adequate antirheumatic agent in individual patients is characterized by 'trial and error', but the development of new biomarkers will hopefully allow to profile individual patients and pick therapies that will have a very high success rate and low risk of toxicity for a particular patient. While we have a long way to go before personalised medicine can be reliably used, we review the available predictors of response for existing biologic antirheumatic agents. We will discuss both environmental / anamnestic factors and potential biomarkers associated with treatment response. In particular, we will review the predictive value of auto-antibodies for therapeutic effectiveness of anti-TNF agents and for RTX, and discuss the potential usefulness of environmental exposures such as tobacco smoking and other RA disease characteristics.

8
AUTOIMMUNITY AND ATHEROSCLEROSIS: VACCINATION AS A THERAPEUTICAL MODALITY

Y. Shoenfeld
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Atherosclerosis is an inflammatory disease, and several antigens have been shown to activate the immune response and affect the development of atherogenesis. This suggests that modulation of the immune system could represent a useful approach to prevent and/or treat this disorder. A vaccination approach might be a useful, effective tool in the modern arsenal of cardiovascular therapy and could possibly be used on a large scale at a low cost. Several modalities of vaccines have been tested against lipoproteins, cholesterol, molecules involved in cholesterol metabolism, atherosclerosis-associated microorganisms, and other molecules (heat shock protein, CD99, vascular endothelial growth factor-receptor, interleukin-2), with promising results. Nevertheless, a deeper understanding of the role of immunization in atherosclerosis will be essential to the use of vaccines in clinical medicine.
Reference:
DE CARVALHO JF, PEREIRA RM R, SHONFELD Y: Vaccination for atherosclerosis. *Clin Rev Allerg Immunol* 2010; 38: 135-140.

9
ACCELERATED ATHEROSCLEROSIS IN RHEUMATOID ARTHRITIS

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Rheumatoid arthritis is a chronic inflammatory disease characterized by a reduced life expectancy mainly due to cardiovascular disease. It is now recognized that the vascular involvement in these patients is mainly due to an acceleration of arterial wall atherosclerotic damage. In long-standing disease, it has been widely demonstrated that both traditional cardiovascular risk and disease-related factors, including chronic inflammation and immune-mediated mechanisms, play a key role in the progression of atherosclerosis. There is also evidence, however, that atherosclerotic damage could start very early in the course of the disease. Since the short- and long-term effects of immunosuppressive treatment on cardiovascular disease outcome is uncertain, a multidisciplinary approach appears to represent the best management of cardiovascular risk in these patients.

10
ACCELERATED ATHEROSCLEROSIS IN SPONDYLARTHROPATHIES

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The cardiovascular mortality in spondyloarthropathies, i.e. ankylosing spondylitis (AS) and psoriatic arthritis (PsA), is elevated and SMR's range between 1.5 and 1.9 for AS and 1.1 to 2.1 for PSA. The cardiovascular morbidity is also increased.
There are remarkably few publications about cardiovascular morbidity in AS. A recent, questionnaire based, study in 600 AS patients revealed an overall prevalence for myocardial infarction of 4.4% versus 1.2% in the general population. AS is also associated with several non-atherosclerotic cardiovascular manifestations as conduction defects and aortic insufficiency.
Cardiovascular morbidity data in PsA are limited. A database investigation revealed 2.5 increased standardized prevalence of myocardial infarction. Moreover, a questionnaire based survey in 750 PsA patients demonstrated that prevalences of ischemic cardiovascular diseases were comparable to that of RA.
The literature indicates that anti-rheumatic therapy has favourable effects on cardiovascular risk factors as well as endothelial function in AS as well as PsA. But whether clinically overt cardiovascular disease is prevented ultimately remains to be shown.
EULAR recommendations for cardiovascular risk management advocate yearly cardiovascular risk screening for patients with AS and PsA. Drug treatment with statins and/or antihypertensives is then dependent on the calculated 10-years CV risk. Finally, effective suppression on the inflammatory process is necessary to further decrease the CV-risk.
Altogether patients with AS and PsA should be viewed as being at an approximately doubled risk for cardiovascular disease. AS and PsA should be acknowledged as a new, independent, cardiovascular risk factors for which cardiovascular risk management is mandatory.

11
PREVENTION AND TREATMENT OF AUTOIMMUNE VASCULAR DISEASE

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The prognosis for patients with systemic autoimmune disease has improved in the past three decades. While vascular injury is essential pathogenic process in some diseases, such as systemic sclerosis (SSc) or systemic vasculitis, others, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) are associated with premature cardiovascular morbidity and mortality, which is attributable to the inflammatory nature of the underlying condition that predisposes to early atherosclerosis. Prevention and treatment of these vascular complications are a great challenge. Therapeutic management of microvascular complications associated with SSc (digital vasculopathy, Raynaud phenomenon, pulmonary arterial hypertension) has been based on the use of prostacyclin analogues, calcium-channel inhibitors and recent development of drugs targeting specific molecules involved in vasoconstriction (endothelin-1, 5-phosphodiesterase). Given that cardiovascular diseases (CVD) may have a major role in the long term prognosis of systemic autoimmune diseases, it is important that we are able to measure the subclinical atherosclerosis in the early phase to predict its development. So all patients should undergo an evaluation for conventional cardiovascular risk factors. Treatment with immunosuppressive, disease-modifying drugs and finally with biological agents (TNF-inhibitors, anti-CD20) has been associated with lower risk of cardiovascular death and morbidity. Therapy with statins potentially may be beneficial for vascular diseases beyond their endothelial preventing and anti-inflammatory effects. Low-dose aspirin is the other recommended pharmacotherapy for the primary prevention of CVD in high risk autoimmune groups. Early recognition of primary and secundary vascular abnormalities has to be our goal to start early treatment for improvement of survival of autoimmune patients.

12
AUTOANTIBODIES AND NEUROPSYCHIATRIC SLE: LESSONS FROM MURINE LUPUS

C. Putterman
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Depression and anxiety are among the most common manifestations of neuropsychiatric lupus (NPSLE). While the mechanism underlying the development of NPSLE is unclear, autoimmunity has been suggested as a primary cause. To investigate the role of gender, we studied lupus-prone MRL/lpr females and males over time and investigated the relation between autoantibodies and the development of NPSLE. MRL/lpr female mice exhibited significant depression as early as 5 weeks of age, when they already demonstrate elevated levels of autoantibodies. In contrast, 5 wo male MRL/lpr mice, with normal autoantibody titers, performed similarly to controls. Depressive behavior was noted only in 18 wo male MRL/lpr mice, when autoantibody titers were elevated. At 5 weeks of age there was a significant correlation of depressive-like behavior with elevated levels of anti-cardiolipin and anti-NMDAR antibodies, while at 18 weeks depression correlated with elevated anti-dsDNA, anti-NMDAR, and anti-ribosomal P antibody titers ($p<0.05$). Both male and female MRL/lpr mice explored more actively than MRL controls in the elevated plus maze test, indicating, paradoxically, less anxiety. Both female and male MRL/lpr mice had normal visual and spatial memory as well as locomotor activity and coordination.
We conclude that female MRL/lpr mice develop CNS dysfunction earlier than male mice, correlating with autoantibody levels. Emotional deficits develop in MRL/lpr female mice with an increase in autoantibody titers already at 5 weeks of age, a time point usually considered to be disease-free. Our results provide further support to a primary role for autoantibodies in the pathogenesis of early neuropsychiatric deficits.

13
PATHOGENIC ROLE OF CYTOKINES IN THE CONTEXT OF GENETIC AUTOINFLAMMATORY DISEASES

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Autoinflammatory diseases (AID) are linked to the excessive activity of cytokines or mediators , whereas diseases due to an insufficient inflammatory response are associated with their lack. The first connection between AID and cytokines was made (1999) in patients manifesting TNF receptor-associated periodic syndrome (TRAPS), likely due to abnormal receptor trafficking mechanisms. Mutations in MVK, encoding mevalonate kinase (1999), lead to the overproduction of IL-1β (hyper-IgD and periodic fever syndrome). The mutation of the "cryoprin" gene encoding a putative pyrin-like protein, causing the familial cold autoinflammatory syndrome (FCAS) and MWS, has led to the discovery of *NLRP3/CIAS1* (gene and NLPR3/cryopyrin (2001). Simultaneously, research on signal transduction and apoptosis suggested that the pyrin domain is part of the death domain-fold family implicated in apoptosis and inflammation (2001). Links were established between the NLRP3/CIAS1 gene, caspase-1 and proIL-1β (2002) and substantiated by evidence. The activation of NLPR3, caspase-1 and subsequent production of IL-1β and IL-18 constitute the concept of what is called "*inflammasome*". NLR proteins signal through different multicomponent *"signalosomes"*, such as "*transcriptosome"* (CIITA),*"inflammasome"* (Caspase1), *"mito-signalosome"* (IFN/cytokine), *"nodosome"* (NF-κB/MAPK activating NOD1/2 complex). The latter is involved in chronic inflammatory bowel diseases (IBD). Not only TNF and IL-1 but also other genetic cytokine abnormalities are involved in AID leading to human diseases such as: IL1Ra deficiency (DIRA, multifocal sterile osteomyelitis), lack of anti-inflammatory IL-10R signaling (severe IBD), hyper-responsiveness to M-CSF and RANKL (cherubism). The role of IL-6 the IL-23/IL-17 axis and IL-33 may account for the diverse clinical manifestations.

14
ANTI-IL-6 RECEPTOR ANTIBODY (TOCILIZUMAB): A B CELL TARGETING THERAPY

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Background: Tocilizumab, a recombinant monoclonal antibody that acts as IL-6R antagonist has been recently introduced for the treatment of rheumatoid arthritis (RA).
Objectives: To evaluate whether tocilizumab therapy may induce B cells to undergo phenotypic changes compatible with a regulatory function.
Patients and Methods: B cells from treated RA patients were isolated before and after 3 months of treatment with tocilizumab and were stained for the expression of intracellular TGF-β, IL-10, membrane CD69, and MHC-II. These markers were assessed in $CD25^{high}$ B cells considered to belong to a regulatory subset of B cells. All markers were expressed in MFI.
Results: DAS improvement was noted three months following the initiation of tocilizumab, namely: from 6.8±0.3 at baseline to 3.1±0.4, $p<0.002$. Clinical benefit was found to occur in association with the expansion of intracellular TGF-β in $CD25^{high}$ B cells (from 5.2 ± 2.3 at baseline to 8.1±2.8; $p<0.02$); In addition, the expression of MHC-II and of CD69 on B cells were significantly reduced from 9.1±2.2 to 4.2±0.4; $p<0.04$, and from 7.6±2.4 to 2.7±0.7; $p<0.03$ respectively.
Conclusions: The present finding of a shift in B cell properties following tocilizumab treatment, namely the increase in TGF-β expression and the alteration in CD69 and MHC-II expression in $CD25^{high}$ B cells, suggests that the expansion of B regulatory cells may be one of the mechanisms by which tocilizumab induces its beneficial clinical effects.

15
MAGNETIC RESONANCE IMAGING IN PSORIATIC ARTHRITIS

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Imaging, in particular magnetic resonance imaging (MRI) and ultrasound, has the potential to transform our understanding of psoriatic arthritis (PsA). PsA is an archetypal type of spondyloarthritis, but may have some feature of rheumatoid arthritis, namely a small joint polyarthritis pattern. Most of these features are well demonstrated on imaging, and as a result, imaging has helped us to better understand the pathophysiology of PsA. Although the unique changes of PsA such as the 'pencil-in-cup' deformities and periostitis are commonly shown on conventional radiography, PsA affects all areas of joints, with enthesitis being the predominant pathology. MRI has allowed us to explain the relationships between enthesitis, synovitis (or the synovio-entheseal complex) and osteitis or bone oedema in PsA.
Current evidence increasingly suggest that the theories related to either autoimmunity directed against shared skin and synovial membrane antigens or some intrinsic angiogenic skin and synovial membrane perturbation, no longer adequately capture the essence of the disease. MRI and pathogenesis studies are supported by recent genetic studies challenging the MHC class 1 link with PsA. Histological studies have complemented the imaging findings, and have corroborated the MRI changes seen in the skin and nails in PsA. The advancement in imaging technology such as high-resolution 'microscopy' MRI and whole-body MRI, and improved protocols such as ultrashort echo time, will further enhance our understanding of the disease mechanisms in PsA.

16
EARLY DIAGNOSIS AND TREATMENT OF PSORIATIC ARTHRITIS

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There are no diagnostic criteria for PsA but only classification criteria. Recently, the CASPAR criteria have been developed by experts from 30 rheumatologic and have collectively been accepted. A major limitation of the CASPAR criteria could be the impossibility of their application in the recent-onset forms, since these were obtained from a population of patients with long-standing disease. However, in the Italian multicenter study on early PsA preliminary results showed sensitivity (91%) and specificity (97.1%) values similar to those of the CASPAR original paper.
In the majority of patients with PsA the skin lesions appear before or at the same time of the musculoskeletal complaints. Therefore, the dermatologist has an exceptional opportunity to identify patients to be sent to the rheumatologist for an early diagnosis of PsA. Some screening tools have been suggested for the identification of the inflammatory manifestations of psoriatic disease to be filled in by the patient in the waiting dermatologic room or at home.
In the last few years, it has been recognized that each inflammatory lesion (joint synovitis, tenosynovitis, dactylitis, enthesitis, sacroiliitis and spondylitis) can develop without symptoms and signs recognizable by the patients and by the physician. Such patients can be considered suffering from sub-clinical or "occult PsA". Their identification represents a further challenge for rheumatology.
To date, no evidence-based treatment strategies are available for early PsA. While rheumatologists await the results of randomized control studies specifically addressing this topic, they should follow the GRAPPA guidelines for treatment of the established forms.

17
SPONDYLOARTHRITIS FROM THE BACK PAIN TO THE HEART INVOLVEMENT

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Ankylosing spondylitis (AS) is a chronic, inflammatory rheumatic disease characterized by inflammatory back pain and radiological evidences of inflammation in sacroiliac and spine joints. However, the disease has some extraarticular manifestations which may lead to severe functional impairment. These extraskeletal manifestations are much more common, than they are estimated among rheumatologists. Uveitis occurs in 20-40% of patients in the course of their disease, while these ratios are 5-10% regarding the clinically manifested inflammatory bowel disease and 1-2% in point of lung diseases.
Cardiovascular events are the most remarkable cause of morbidity and mortality in AS patients. Beyond the traditional risk factors of atherosclerosis, clear links have been established between the chronic inflammation and the cardiovascular diseases. The identification of predisposing factors for atherosclerosis and the early detection of endothelial dysfunction by flow-mediated vasodilatation or macrovascular discrepancies by common carotid intima-media thickeness and pulse wave velocity may be crucially important in the prevention of early mortality in AS.

18
IDIOPATHIC RECURRENT PERICARDITIS: IDIOPATHIC, AUTOIMMUNE OR AUTOINFLAMMATORY

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The etiology and pathogenesis of idiopathic recurrent acute pericarditis (IRAP) remain controversial standing like a bridge that crosses infectious, autoimmune and autoinflammatory pathways. Anything may cause acute pericarditis, but in 85% of cases it remains "idiopathic". Recurrences occur in up to 20-50% of patients. An immuno-mediated pathogenesis is suggested by the presence of pro-inflammatory cytokines in pericardial fluid, the presence of antinuclear autoantibodies in sera, the occurrence of new autoimmune diagnoses and the good response to anti-inflammatory or immunosuppressive therapy. Recently, anti-heart (AHA) and anti-intercalated-disk (AIDA) was found increased in IRAP patients. Moreover, IRAP mimicks hereditary periodic fever syndrome, particularly tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS). Familial clustering of pericarditis, together with a poor response to colchicine administration, might also represent a clue for investigating mutations in the *TNFRSF1A* gene in patients with IRAP, and may eventually disclose TRAPS.
Whatever the etiology is, we recommend nonsteroidal anti-inflammatory drugs (NSAIDs) at high dosages, till the resolution of symptoms and normalization of C-reactive protein and erythrocyte sedimentation rate. Corticosteroids should be used rarely, at low doses, with an extremely low tapering and with osteoporosis prevention. Colchicine leads to a clinically important and statistically significant benefit, reducing recurrences by 50%.

19
HOW TO MANAGE PATIENTS WITH CHRONIC, APPARENTLY UNACCOUNTABLE, INCREASE OF CK

E. Pegoraro
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HyperCKemia may be defined as values beyond 1.5 times the upper normal limit. This definition will exclude from further testing the 2.5% of normal individuals showing asymptomatic, slight increased value of CK and it will prevent them from useless investigations. With this caveat hyperCKemia deserves a diagnostic approach. First, the non-myopathic causes of increased level of CK should be investigated. Medications (statins, fibrates, anti-psychotic drugs, etc), endocrinopathies such as hypothyroidism, alcoholism, strenuous exercise, trauma, metabolic disorders, chronic cardiac disease, infections and malignancies must be ruled out by clinical history and first level blood work-up. Second, pauci-symptomatic (patients who have non-specific neuromuscular signs) and asymptomatic hyperCKemia patients may be identified and will be eligible for a muscle biopsy. In the literature the percentage of final diagnosis after muscle biopsy varies from 16% to 63%. There are several variables that may increase the likelihood of reaching a specific diagnosis: CK values >10 times normal, abnormal EMG, age below 15 years, exercised-induced pain or exercise intolerance as presenting symptoms. The most frequently identified diseases after muscle biopsy are glycogen storage diseases, muscular dystrophies, and inflammatory myopathies. The diagnosis of idiopathic hyperCKemia will be limited to those patients in whom all investigations reult normal.

20
SHOULD WE BE NERVOUS ABOUT AUTOIMMUNE DISEASES?

Z. Szekanecz
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This state-of-the-art lecture will consist of three major parts.
First, the major neuro-psychiatric manifestations of autoimmune diseases including SLE, the antiphospholipid syndrome, rheumatoid arthritis and systemic vasculitides will be reviewed in short.
Second, new data on chronic fatigue syndrome and the fibromyalgia-group will be summarized. It seems that fibromyalgia, chronic fatigue syndrome and related disorders including silicon implant-associated syndrome (SIAS), Gulf war syndrome (GWS), multiple chemical sensitivity syndrome and myofascial pain syndrome may have a lot in common. All these disease states have been associated with depression, chronic pain and other neuro-psychiatric manifestations. Infections and vaccination, including the use of adjuvants and chemicals have been implicated in the pathogenesis of these disorders. Hence, the group of these diseases has been designated as Autoimmune Syndrome Induced by Adjuvant (ASIA) or Shoenfeld-syndrome.
Finally, the use of some biologics including rituximab, natalizumab and efalizumab have been associated with the development of progressive multifocal leukoencephalopathy (PMLE) in some patients. Recent data regarding this JC virus-mediated disease will also be presented.

21
ARE ANTI-P ANTIBODIES ASSOCIATED WITH NPSLE?

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Neuropsychiatric (NP) involvement occurs in up to 80% of patients with systemic lupus erythematosus (SLE), and include neurological syndromes of central, peripheral as well as autonomic nervous systems. The pathogenesis of the broad spectrum of NPSLE manifestations is still unknown, but several autoantibodies directed to neuronal or ubiquitary antigens have been suggested to play a role.
Anti-ribosomal P (anti-P) antibodies are directed to the functional centre of ribosomal P (phosphorilated) proteins. Anti-P antibodies are considered a specific marker of SLE and appear to be associated with disease activity, liver, kidney, and, especially, NP involvement. However, anti-P serology has not been included in the recently revised ACR criteria for SLE classification.
One of the most intriguing aspects of anti-P antibodies is their pathogenic and predictive role in specific NPSLE manifestations, mostly psychosis and depression. Intracerebroventricular injection of anti-P antibodies induces depression-like behaviour and olfactory dysfunction in mice. Injected anti-P antibodies specifically stain neurons in areas of the limbic system. In addition, anti-P antibodies from NPSLE patients target a novel neuronal surface P protein and induce neuronal cells apoptosis by increasing intracellular calcium influx.
As regards the predictive value of anti-P antibodies in NPSLE, prospective studies are more informative on this concern, and a longitudinal evaluation of both anti-P antibodies and NPSLE occurrence in our inception cohort of 219 SLE Italian patients, followed-up for over 10 years, confirmed that anti-P antibodies are associated with psychosis and firstly demonstrated that they may be present also in patients with peripheral nervous system complications.

22
EPIGENETIC REGULATION

S. Gay
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During the last decade an explosion of new data has emerged in molecular biology about "Epigenetics". Epigenetic regulations of gene expression are mediated by modifications of DNA and its associated chromation proteins without changes to the DNA sequence. Biochemical processes of acetylation, methylation as well as sumoylation in concert with miRNAs (microRNAs) are in the limelight of current research. With respect to rheumatology, Bruce Richardson´s group in Ann Arbor,

Michigan has first shown that T cell subsets in SLE are in certain promoters hypomethylated. We have demonstrated that in rheumatoid arthritis (RA) synovial fibroblasts are not only effectors cells, but aggressively invading cells participating in the spreading of the disease (1). In searching for the endogenous activation of these cells we found that RASF are hypomethylated and reside in a hyperacetylated synovial environment (2). Moreover, numerous dysregulated expressions of miRNAs have been detected resulting in the modulation of matrix-degrading enzymes and of proinflammatory chemokines and cytokines (3).

References:

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23
WHAT IS MORE RELEVANT IN THE INDUCTION OF AUTOIMMUNITY?: ENVIRONMENT

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Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and inflammatory bowel disease have complex pathogeneses and likely multifactorial etiologies. The current paradigm for understanding their development is that disease is triggered in genetically-susceptible individuals by exposure to environmental factors. Some of these environmental factors have been specifically identified, while others are hypothesized and not yet proven, and it is likely that most have yet to be identified. I will review the evidence concerning known and hypothesized environmental risk factors for autoimmune diseases, including, among others: cigarette smoke, crystalline silica, oral contraceptives and postmenopausal hormone use, sunlight and vitamin D, EBV, dietary factors and early childhood exposures, and environmental air pollution.

24
THE ROLE OF SYNOVIAL BIOPSY IN THE DIAGNOSIS OF INFLAMMATORY ARTHRITIS

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Inflammatory arthritis is among the most important chronic inflammatory disorders. Particularly at presentation, early in the course of the disease, it might be difficult to classify the disease in specific diagnostic and prognostic categories and the diagnosis of undifferentiated arthropathy is made in 30-40% of patients. Even when the diagnosis of early RA is made, clinically, this is a heterogeneous condition with a variable course and major differences in joint damage scores: 10-12 fold after 10 years of disease (1). Thus, it remains a critical unmet need to be able to be able to identify patients with poor prognosis in order to tailor treatment on an individual patient basis to prevent disability and the consequent considerable costs for individuals and society. This is also vital for targeting limited health care resources using expensive biologic drugs.

In this lecture, the hypothesis that there are distinct molecular and cellular phenotypes within the synovial tissue that define specific disease subsets and provide characteristic prognostic implications will be discussed.

In addition, the discussant will debate the clinical utility of using minimally invasive ultrasound (US) guided synovial biopsy (2), similarly to other medical specialties (i.e. nephrology, gastroenterology and oncology), to stratify patients in individual prognostic categories permitting earlier evaluation of structural damage progression and response to therapy.

Finally, this talk will explore the opportunity of using histopathology and molecular characterization to improve on currently employed composite clinical assessment tools in clinical trials, particularly in early phase development and proof of concept (3).

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EARLY TREATMENT IN UNDIFFERENTIATED EARLY ARTHRITIS

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Studies have shown that patients diagnosed and treated early have a better long-term outcome as well as disease-associated morbidity and, potentially, mortality. The presence of anti-CCP Abs has been shown to identify a population at increased risk for aggressive, erosive disease, thus, potentially identifying those most likely to benefit from this early aggressive therapy. The introduction of many new effective therapies over the past decade, shows that it is imperative to identify subjects who will develop more severe disease as early as possible to have the opportunity to receive aggressive therapy. Many Authors argue that early undifferentiated arthritis may remit in those subjects not yet meeting current rheumatoid arthritis (RA) criteria. An alternative view suggests that if a diagnosis of RA can be confirmed sufficiently early to allow institution of aggressive therapy, sustained remission may be attained in those who would have otherwise progressed to chronic disease.

26
ABATACEPT: ITS ROLE AS FIRST LINE BIOLOGIC AGENT

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Abatacept blocks the activation of T cells by interrupting the interaction between the CD28 ligand on the T cell and the CD80/86 ligand on the antigen presenting cell. Inhibition of T cell activation, that play important role in the pathogenesis of RA, has pleotropic effects that lowers the downstream production of multiple cytokines The clinical efficacy of abatacept is comparable to anti-TNF agents and, in one comparison trial, proved to be superior to infliximab at standard doses. The safety profile of abatacept is excellent, with fewer SAEs than anti-TNF agents, can be used in patients with co-morbidities that preclude the use of anti-TNF agents. Responders may show improvement as soon as in 1 month and, in responders, improvement is seen in all ACR core components by month 4. Patients who respond to abatacept tend to maintain their clinical responses over time, with little evidence of tachyphylaxis or antibody-mediated drug resistance. Inhibition of radiographic progression falls short of that seen with anti-TNF agent but is robust and quite adequate to prevent loss of function. Abatacept should be strongly considered as first-line therapy of patients with early RA who also exhibit an incomplete response to MTX.

27
CURRENT USE OF METHOTREXATE IN RHEUMATIC DISEASES

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The use of methotrexate (MTX) as a therapy for rheumatic diseases started initially from positive case reports, uncontrolled case series and then several decades later from placebo controlled studies and active comparator studies. MTX has now the most well-studied DMARDs and the most popular drug worldwide in the treatment of RA. It is the first-line DMARD in RA with over two decades worth of excellent long-term efficacy and safety. It like other DMARDs improve the symptoms of joint pain and swelling, but more importantly, prevent the progression of joint damage. However, there is significant variability in patients` response to MTX, both in efficacy and toxicity. In ankylosing spondylitis (AS), the use of MTX is not recommended for the axial manifestations and may have some efficacy in the peripheral involvement. Furthermore, there is no evidence that MTX increases the effects or prevents the side effects of TNF-blockers if given in combination. MTX remains one of the most commonly used medications in the treatment of patients with psoriatic arthritis (PsA). There is no convincing evidence that MTX is beneficial in primary Sjögren`s syndrome. There are randomised controlled trials showing the benefit for MTX on overall SLE activity, reduction in glucocorticoid doses, and effects on lupus arthritis and lupus skin manifestations. MTX may be helpful in vasculitis, haematological manifestations, and perhaps kidney disease. Furthermore, most patients with dermatomyositis or polymyositis are treated with oral high-dose prednisone combined with azathioprine or MTX to facilitate tapering of prednisone.

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RHEUMATOID ARTHRITIS: FROM ARTHRITIS TO HEART ATTACK

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Higher mortality in rheumatoid arthritis (RA) in comparison to the general population is largely attributable to cardiovascular disease (CVD), particularly coronary atherosclerosis but also to non-fatal myocardial infarct and heart failure. Inflammatory and immune-mediated mechanisms play a central role in both atherosclerosis and RA, and have a number of common pathogenetic mechanisms. Chronic inflammation can promote endothelial cell activation and vascular dysfunction, leading to noncompliance of vessels and development of atheroma. However, the reasons for the dramatic increase in atherosclerotic CVD in RA are not totally understood and appear to be complex. An expanded population of CD4+ -CD28 T cells has been demonstrated in the peripheral blood of patients with RA, and clonal expansion of a similar T-cell subset has been reported in the blood and atherosclerotic plaques of patients with unstable angina. TNF, an inflammatory cytokine, promotes inflammatory responses that are important in the pathogenesis of RA. However, TNF promotes dyslipidaemia and insulin resistance, both of which are traditional risk factors for atherosclerosis; it upregulates adhesion molecules, leading to fatty streak formation and the initiation of atherosclerosis, and it is involved in the inflammation leading to plaque rupture. TNF may also promote thrombophilia, encouraging thrombotic events. IL-6 a pro-inflammatory cytokine that stimulates hepatocytes to synthesize acute phase response proteins such as CRP and fibrinogen may also contribute to atherosclerosis and arterial thrombosis by enhancing endothelial cell adhesiveness, activating the production of tissue factor, fibrinogen and factor VIII, increasing platelet production and aggregation and by decreasing endogenous anticoagulant levels.

Oral Presentations

29
PREVALENCE OF ANTI-ANNEXINE XI ANTIBODIES IN PATIENTS WITH AUTOIMMUNE RHEUMATIC DISEASES

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Anti-annexin XI antibodies (A-XIAb) have been found in sera from patients with autoimmune rheumatic diseases (ARD) such as systemic lupus erythematosus (SLE), primary Sjögren syndrome (SS), and rheumatoid arthritis (RA); however a correlation with specific autoantibodies or clinical features has not been demonstrated.
Aim of the study: To identify clinical and serologic features of patients A-XIAb positive.
Patients and methods: We studied 428 consecutive patients with ARD: 150 SLE, 64 idiopathic inflammatory myositis (IIM), 26 systemic sclerosis, 23 SS, 17 RA, 77 undifferentiated connective tissue disease (UCTD), 42 overlap syndrome and 74 healthy subjects. A-XIAb were detected with immunoblotting using Raji cells as substrate. Clinical charts of positive patients were retrospectively reviewed.
Results: Nine patients (2%) were A-XIAb positive, 8 female and 1 male, mean age (±SD) 55.2±6.3 years (range 46-66), mean disease duration 132.7±112.5 months (range 2-309). Three patients were affected with IIM, 3 with SLE (2 with skin manifestations), 2 with UCTD, 1 with SS. All healthy subjects were A-XIAb negative. Prominent clinical and serological features were: arthralgias (67%), muscle asthenia (56%), arthritis (45%), cutaneous manifestations (33%), low C3 (100%), low C4 (83%), leuco/lymphopenia (62%), thrombosis (10%), ANA positivity (100%), anti-SSA positivity (44%), anti-phospholipid antibodies positivity (43%).
Conclusions: A-XIAb are rare in patients with ARD and no association with specific clinical or serological features was found. A-XIAb is an additional marker of autoimmunity, characterized by low sensitivity, and not specific for any ARD.

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PATHOGENETIC AND PROTECTIVE AUTOANTIBODIES INVOLVED IN LUPUS GLOMERULONEPHRITIS

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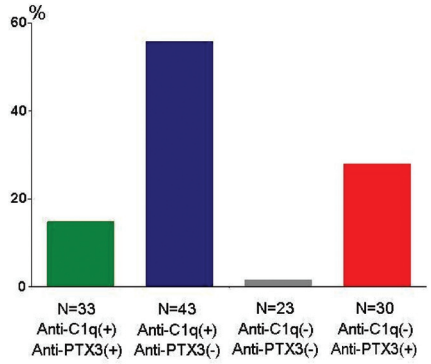
Our aim was to evaluate the relationships between glomerulonephritis and some autoantibodies in SLE patients.
The serum samples of 130 consecutive SLE patients and 130 healthy controls, age- and sex-matched, were evaluated for the presence of anti-PTX3 and anti-C1q by home-made ELISA tests: plates coating with PTX3/PBS for anti-PTX3 or C1q/carbonate buffer for anti-C1q (5µg/ml); sera dilution 1:200 and anti-human IgG dilution 1:10000 in 1%BSA/PBS for anti-PTX3 or 1%BSA/PBS+Tween-20+1M NaCl for anti-C1q. Anti-dsDNA were detected by commercially avaliable kits.
Prevalences and levels of anti-PTX3 and anti-C1q were significantly higher in SLE patients than in healthy controls ($p<0.001$, for all). Associations between anti-PTX3, anti-C1q or anti-dsDNA and glomerulonephritis in SLE patients are reported in Table.

	Glomerulonephritis		
	Yes	No	*p*
Anti-PTX3			
Levels (mean OD±SD)	0.176±0.120	0.387±0.211	0.001
Prevalence (%)	24.6	65.2	0.001
Anti-C1q			
Levels (mean OD±SD)	0.738±0.576	0.418±0.231	0.001
Prevalence (%)	72.1	48.3	0.025
Anti-dsDNA			
Levels (mean OD±SD)	0.610±0.502	0.426±0.219	0.011
Prevalence (%)	67	33	0.001

Notably, the prevalence of glomerulonephritis was significantly higher in anti-C1q(+)/anti-PTX3(-) patients and lower in anti-C1q(-)/anti-PTX3(+) patients (see Figure).



No other relevant relationships were found.
In the development of glomerulonephritis anti-C1q and anti-dsDNA seem to be pathogenic, whereas anti-PTX3 protective.

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RENAL INFLAMMATORY INFILTRATE IN LUPUS NEPHRITIS PATIENTS

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Objective: To evaluate the presence and phenotype of the interstitial inflammatory infiltrate in renal tissue of SLE nephritis patients and possible relationships with clinical, histological parameters and treatment response.
Methods: 31 consecutive patients with newly diagnosed lupus nephritis were evaluated for demographic, clinical, immunological, renal evolution data and with renal biopsy. Tissues were stained also with cellular markers CD3, CD20, CD68 (cell count was expressed as n/mm^2). Patients were divided in responder (R) and non responder (NR) subgroups at sixth month of therapy.
Results: Characteristics of the 31 patients are: 27 women, age at renal biopsy 35.6±11.6, number of class IV WHO=31, activity index 9.1±4.3 and chronicity index 2.1±1.9. In our series, macrophages were the main class of immune cells infiltrating the kidney (CD68+:9.1±9.6/mm^2), followed by T (CD3+:3.0±4.0/mm^2) and B lymphocytes (CD20+:2.2±3.4/mm^2).
Chronicity index directly correlated with CD3+ cells presence (r=0.5, p=0.004).
17/31 (54.8%) renal biopsies had a significant interstitial infiltrate and 14 had a poor or none infiltrate. 13/14 patients without infiltrate were responder with respect to 10/17 with infiltrate (93% vs 59%, p=0.04).
Responder patients (n=23) differ from non responder only for the presence of inflammatory infiltrate (43.5%vs87.5%, p=0.04) and the number of CD3+ cells (p=0.03).
On the multivariate analysis, the interstitial infiltrate resulted the independent predictive parameter of response (p=0.05; OR 9.1, 95%IC 1.0-86.1).
Conclusion: These data supported the hypothesis that the cell-mediated immunity play a central role in the SLE nephritis pathogenesis and that interstitial infiltrate may have a role in the nephritis progression up to chronic damage.

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THE PARADIGM OF ANTISYNTHETASE SYNDROME: DIFFERENT MANIFESTATIONS WITH DIFFERENT TIME OF ONSET

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Background: Anti-synthetase syndrome (AS) is a connective tissue disease characterized by the occurrence of manifestations such as arthritis, interstitial lung disease (ILD) and myositis, together with anti-synthetase antibodies positivity. Recently incomplete forms of AS (eg only ILD and anti-synthetase antibodies positivity) have been described.
Study purpose: To assess the prevalence of incomplete AS and the variation overtime of clinical profile in these patients.
Patients and methods: All patients referring to our Division and diagnosed with AS were reassessed for clinical profile at disease onset; we recorded also the appearance of other AS-related manifestations during follow-up.
Results: Eighteen patients (5 males/13 females) were enrolled. Median age at AS onset was 52.5 years (IQR:45-69), median follow-up 65 months (IQR:31.5-91.5). All patients were anti-Jo1 positive. Onset manifestations were: arthritis+ILD+myositis in 8 patients, arthritis in 5, arthritis+ILD in 3, arthritis+myositis in 1, ILD in 1. The 5 patients presenting with arthritis subsequently developed myositis and ILD (range of delay: 3 months to 13 years), the patient presenting with ILD developed arthritis after 21 months of follow-up, only 1 patient presenting with arthritis+ILD developed myositis (delay: 2 years). No other oatients changed disease clinical profile during follow-up.
Conclusions: The timing of clinical finding presentation in AS patients is variable, with delays ranging from few months to several years. In fact, although the majority of AS experienced arthritis, myositis and arthritis, less than 50% of our patients presented these manifestation since the beginning. Thus our data indicate the need of an extended follow-up in patients with incomplete AS.

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POLYMYALGIA/HORTON´S ARTERITIS AFTER INFLUENZA VACCINATION: A NEW "ASIA" SYNDROME? EXPERIENCE OF 10 CASES

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Polymyalgia Rheumatica (PMR) Horton's Arteritis (HA) is a common inflammatory rheumatic disease in people over the age of 50 years, characterized by pain and morning stiffness in the shoulder and pelvic girdles, along with evidence of an underlying inflammatory reaction. There has been reported the association of PMR with HLA-DRB1*0401 and DRB1*0404 alleles, and there is a small number of reports of PMR following influenza vaccination (IV) in genetically predisposed subject having alleles at HLA-DRB1 locus.
Recently, a new syndrome called 'ASIA'-autoimmune/auto-inflammatory syndrome induced by adjuvants has been proposed. We report 10 cases of previously healthy patients who developed PMR/HA, within 2-4 months after IV. Immune adjuvants may play a key role in induction of post-vaccination adverse events such as, in our cases, a vasculitis-related disease. On the other hand, a role of the individual susceptibility has to be valued, which can justify the rarity of the events, despite the several kind of environmental factors (i.e. infectious triggers, "natural adjuvants", etc.). Furthermore, the identification of an individual susceptibility to post-vaccination adverse events, by studying the HLA system as well as Toll-like receptor signalling pathways, could be useful to clarify the correlation between molecular mechanisms and clinical patterns of the new 'ASIA' syndrome.

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DOES CERTAIN TYPE OF ANTIBODY IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME INFLUENCE ACUTE CORONARY SYNDROME DEVELOPMENT?

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Antiphospholipid antibodies (aPL) have been implicated in the pathogenesis of coronary artery disease (CAD). The potential role of a specific type of aPL in the atherosclerosis development is rather controversial. The aim of our study was to evaluate the correlation of the presence of a certain type of aPL with the occurrence of myocardial infarction (MI) or unstable angina pectoris (UAP) in patients with antiphospholipid syndrome (APS). 256 APS patients were analyzed: 162 patients with primary APS (PAPS) and 94 patients with systemic lupus erythematosus (SLE) and secondary APS (SAPS), in which the data was collected on the occurrence of MI and UAP. The type (aCL IgG, aCL IgM, β_2GPI IgG, β_2GPI IgM, LA) of aPL was analyzed considering MI and UAP presence and patients were divided into three groups regarding the number of positive aPLs (one, two or three and more). PAPS and SLE patients did not differ among themselves with regard to the occurrence of MI (p=0,102) and UAP (p=0.123). Considering type of aPL, in all APS patients as well as in PAPS in SAPS separately, there was no significant difference. In a PAPS group with two aPL positive 23.2% of patient had UAP comparing to 8.8% in a group with one aPL positive (p=0.017).
The presence of a certain aPL type had no impact on the occurrence of MI and UAP in patients with PAPS and SAPS but the number of positive aPL presented was significantly related to UAP occurrence in PAPS patients.

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DOES CERTAIN TYPE AND LEVELS OF ANTIPHOSPHOLIPID ANTIBODIES INFLUENCE THROMBOSIS? RESULTS FROM THE SERBIAN NATIONAL COHORT STUDY

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Introduction: Thrombosis are the most frequent clinical manifestation of APS with the presence of various levels of antiphospholipid antibodies (aPL).
Patients and methods: The analyzed cohort (Serbian National Registry) comprises a total of 256 patients (162 PAPS and 94 SLE). aPL analysis included detection of LA and aCL, β_2GPI (IgG/IgM). The objective was to observe the prevalence and localization of thrombosis, and correlate it to aPL type and level in patients diagnosed with pAPS or sAPS.
Results: Thrombosis was diagnosed in 119 (46.5%) patients, with higher prevalence in pAPS compared to sAPS patients (51.2% and 38.3%, respectively, p=0.045). There was similar prevalence of arterial thrombosis in both groups (34.6% and 34%, respectively, p=0.932) although venous thrombosis was more frequent in PAPS (25.9% and 8.5%, respectively, p=0.001**).** Thrombosis was observed in 92 (55.8%) patients who had more than one type of antibodies (category I), in 13 (41.9%) patients with category IIa, in 19 (46.3%) patients with category IIb, and in 73 (44.2%) patients with category IIc (p=0.10). There was no statistically significant difference in the prevalence of arterial/venous thrombosis in patients with low/normal, intermediate, and high levels of aCL and anti-β_2GPI (IgG, IgM). Older age in APS patients is a risk factor for thrombosis (median age 49.8 and 39.8, respectively, p=0.001).
Conclusion: The prevalence of venous thrombosis was higher in the PAPS group. Antibody category and levels of various types of antibodies did not correlate with the prevalence of thrombosis in the Serbian National Cohort Study.

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NEUROPSYCHIATRIC DISORDERS IN THE ANTIPHOSPHOLIPID SYNDROME

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In Antiphospholipid syndrome (APS) central nervous system involvement may occurs with neuropsychiatric disorders with or without ischemic events or multi-infarct dementia. In most cases, the brain MRI shows non-specific areas of gliosis in subcortical and/or cerebellar white matter due to decreased perfusion. The hippocampus involvement, due to high sensitivity to hypoxic-ischemic damage, leads to the typical memory loss.
The aim of this study is to investigate the prevalence of non-thrombotic neurological manifestations and psychiatric disorders in a APS series.
We describe 22 patients with primary or secondary APS; they were subjected to psychometric neuropsychological tests to detect depressive and anxiety disorders, memory and neurocognitive deficits; neuro-imaging techniques were administered, in presence of neurological disorders.
We found a significant relationship between disease duration and structural MRI anomalies, so in long-term cases there is a widespread cortical atrophy. There was also an association between psychiatric and neuropsychological abnormalities test and auto-antibody levels.
Thrombotic ischemic brain damage does not explain all the neuropsychiatric manifestations of APS; We assumed that was a direct damage mediated by aPL. This type of damage may cause depressive disorders, even if they may be simply a psychological reaction of suffering from a chronic disorder, or side effects of corticosteroid therapy, used mainly in patients with secondary APS.
Theses results highlighted the importance of the detection of neuropsychiatric manifestations, through the use of psychometric neuropsychological tests, in order to promptly establish an effective therapy with antiplatelet and/or anticoagulants, and prevent progression to more severe neurological and psychiatric disorders

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NEW CHALLENGE IN CAPILLAROSCOPY: IS FEET NAILFOLD CAPILLAROSCOPY USEFUL IN CLINICAL PRACTICE?

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Background: Nailfold capillaroscopy (NFC) is a simple and non-invasive method useful in clinical practice to distinguish between primary and secondary Raynaud´s phenomenon (RP).
Objectives: The aim of the study was to compare quantitative and semi-quantitative NFC parameters (cutaneous transparency, venous plexus, length, disorganization of the microvascular array, capillary ramifications, micro-haemorrhages, angiogenesis, ectasia, micro-aneurisms, giant capillaries, blood flow velocity, avascular areas) observed in hands and feet of patients with systemic sclerosis (SSc) and non-SSc control group and to identify the usefulness of the feet NFC in routine clinical practice.
Methods: NFC was performed in a total of 61 subjects [16 with diagnosis of SSc, 15 with primary RP, 15 with rheumatoid arthritis and 15 healthy controls]. Videocapillaroscopy was performed using "Video Cap" (DS MEDICA with 100x optical probe) in according with the current guidelines.
Results: Compared the results of hands and feet NCS in non-SSc patients, findings were found similar both in hands and feet, except for cutaneous transparency (χ2=4,444 p=0.035), blood flow velocity (χ2=16,576 p<0.005) and tortuosity (χ2=6,429 p=0.011).
Analyzing SSc patients, significant differences were observed comparing hands and feet NFC in micro-haemorrhages (χ2=7.385 p=0,007), micro-aneurisms (χ2=13,333 p<0,005) and giant capillaries (χ2=18,286 p<0,005); in SSc patients feet, giant capillaries were detected only in one of them and no micro-haemorrhages were found.
Conclusion: NFC of the feet compare to NFC of the hands is less useful to recognize giant capillaries and micro-haemorrhages and for this reason we don´t suggest it as a valid instrument in clinical practice.

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CXCL13 - A PUTATIVE BIOMARKER IN SYSTEMIC SCLEROSIS

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Introduction/objective: In systemic sclerosis (SSc), the B-cell activating factor BAFF has been shown to be elevated in serum and to correlate with skin score. BAFF mediates the migration of B-cells in response to the B-cell chemokine CXCL13. CXCL13 has not yet been investigated in SSc. Our aim was to investigate serum levels of CXCL13 and BAFF in SSc and their clinical association in SSc patients.
Patients and methods: CXCL13 and BAFF serum levels from 48 patients with SSc, 9 patients with primary Raynaud's syndrome, 16 patients with circumscribed scleroderma and 30 blood donors were analyzed by ELISA. Results were compared with clinical and laboratory characteristics, and the correlation of CXCL13 and BAFF in SSc was assessed.
Results: Serum CXCL13 and BAFF levels were significantly higher in patients with SSc than in healthy blood donors. CXCL13 and BAFF levels were also significantly elevated in morphea patients. CXCL13 values were higher in patients with limited SSc than in diffuse SSc, and correlated with the incidence of pulmonary hypertension and elevated ESR. Patients under immunosuppressive therapy had lower BAFF levels, but higher CXCL13 levels than SSc patients without immunosuppressive therapy.
An association of BAFF with skin sclerosis could not be confirmed, and there was no correlation of CXCL13 and BAFF elevation.
Conclusions: Elevated CXCL13 levels might be an indicator for disease activity and lung involvement, whereas BAFF levels show an association with immunosuppressive therapy. Markers of B-cell activation could be used as further classification criteria and as potential therapeutic targets in SSc.

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IMPRESS: ITALIAN MULTICENTRIC STUDY OF PREGNANCY IN SYSTEMIC SCLEROSIS

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Objective: We assessed fetal and maternal outcomes in Systemic sclerosis (SSc) women.
Patients and methods: A retrospective analysis of prospectively collected data were done in 26 Italian centers.104 SSc women were observed during their 116 pregnancies and compared to general obstetrical population (GOP, 3939 deliveries).
Results: In SSc patients preterm deliveries (29% vs 12%) and severe (<34 weeks) preterm delivery (10% vs 5%), intrauterine growth restriction (5% vs 1%) and very low birth weight babies (6% vs 1%) were significantly more frequent than in GOP. Patients with a preterm delivery were taking folic acid supplementation in a smaller proportion (32%) than those who had a term delivery (63%). Antitopoisomerase and anticentromere antibodies were not significantly associated with different pregnacy outcomes, such as diffuse and limited disease. A significantly higher prevalence of miscarriages was reported by the same patients in previous anamnestic pregnancies (26% vs 3%). The disease remained stable in most SSc patients, but we observed 4 cases of disease evolution within 1 year from delivery, all in antitopoisomerase positive patients.
Conclusions: SSc patients can have successful pregnancies, but they have an increased risk of preterm delivery, intrauterine growth restriction and very low birth weight babies. A disease evolution during or after pregnancy is a rare but possible event. High-risk management should be standard in these patients and pregnancy should be avoided in cases of severe organ damage and postponed in early diffuse SSc.

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THE ROLE OF B-1A B CELLS IN PREGNANCY

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Pre-eclampsia (PE) is a devastating pregnancy-associated disorder characterized by the onset of hypertension, proteinuria, and edema affecting around 5-8 % of pregnant women. The etiology and physiopathology of PE remain unknown. Recently, autoantibodies were proposed as responsible for its onset. Despite much information regarding autoantibodies, no attention has been focused so far on the cells involved in antibodies production in PE. B-1a B cells express the surface marker CD5 and produce so-called "natural antibodies" which are polyreactive, potentially autoreactive and therefore interesting candidates to produce autoantibodies involved on the onset of preeclampsia. The main goal of this work was to document the dynamic of B-1a cells throughout normal pregnancy (NP) in humans and to analyze whether they are modified immediately after the onset of PE. We observed that the proportion of B-1a cells in peripheral blood does not change with the establishment of pregnancy and remains stable throughout the first trimester and second trimester. NP women at their third trimester, however, present a dramatic diminution in the proportion of B-1a cells. These changes can not be observed in PE patients, who present even higher levels of B-1a cells than non-pregnant or pregnant women at their first or second trimester of pregnancy. A soluble factor present in NP and absent in PE patients regulate the phenotype of these cells. Our results suggest that B-1a B cells have a prominent role in the pathology of PE, probably by producing autoantibodies responsible for the symptoms of this disease.

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OPTIMISED CORTISOL TREATMENT OF RHEUMATOID ARTHRITIS BASED ON THE CIRCADIAN RHYTHM OF KEY FACTORS

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The conference CORA is an ideal place to define new concepts. Based on our recent article in Arthritis & Rheumatism (60, 2009: 2585-2594) we develop a mathematical model for the circadian variation of key factors in rheumatoid arthritis (RA) and show how the model can be used to optimise treatments. The interaction network of the key factors tumour necrosis factor (TNF), cortisol, cholesterol, noradrenaline (NA), and presynaptic NA store was validated with world circadian data from healthy individuals and rheumatoid arthritis patients. Deregulations that transform the circadian variation from healthy to RA were investigated in silico and it was found that all mechanisms depending on TNF have adapted their sensitivity regime to the overall higher TNF level. We find back in the in silico networkthe phenomenon of inadequate cortisol secretion relative to the plasma TNF level as well as the depletion of cholesterol stores. Finally, the RA treatment with cortisol was investigated in silico and it is found that the same dosis of cortisol leads to an up to three-fold effect on the day average of TNF depending on the time point of administration. This surprisingly pronounced effect was now also found in the pharmaceutical industry.
These first in silico studies of the neuroendocrine-immune system in rheumatology demonstrate that computational biology in medicine, making use of experimental data and expert knowledge, supports understanding of the pathophysiology of complex nonlinear systems. In addition, we show that in silico models can guide clinical research to develop more efficient treatment protocols.

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NOVEL PEPTIDES AS POTENTIAL TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a loss of immunologic tolerance, production of auto-antibodies and inflammatory damage in multiple organs. We have tested the effect of anti-inflammatory peptide, a H2A histone fragment, termed IIIM1 on MRL/lpr mice, an animal model of SLE. Oral administration of IIIM1 at early stage of disease caused reduction in proteinuria and serum anti-dsDNA antibodies. Starting the treatment at advanced stage of disease resulted in prolonged animal survival, decreased lymphadenosis and reduced levels of pathogenic or abnormal double negative $CD4^-CD8^-$ cells and $B220^+$ cells in lymph nodes and spleen. We discovered that IIIM1 induces the production of an additional peptide, a fragment of alpha-1-antitrypsin, termed UBE. Relatively low dose (1μg/kg) of UBE reduced proteinuria and hematuria in MRL/lpr mice. The beneficial effect of the peptide was corroborated by histological examination. Furthermore, a significant reduction in serum IL17, IL12 and anti dsDNA antibodies was observed in the UBE-treated mice. Isolated CD4 cells incubated with the peptide showed similar cytokine profile. Decreased levels of double negative $CD4^-CD8^-$ and $B220^+$ cells were determined in lymph organs of UBE-treated animals. The beneficial effects of both UBE and IIIM1 suggest these peptides as potential drugs for SLE.

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IS DSDNA VACCINATION TO ACTIVATE $CD4^+CD25^+$ SUPPRESSOR/REGULATOR T CELLS IN LUPUS A FEASIBLE TREATMENT ?

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$CD4^+$ $CD25^+$ FOXPro3 Suppressor/Regulator T cells (T Regs), are depressed in function or in numbers in SLE[1], Rheumatoid Arthritis,[2] recurrent pregnancy loss,[3] Multiple Sclerosis[4], Crohns Disease and Colitis,[5] Psoriasis,[6] Aging[7], Alzheimers Disease,[8] Transplantation rejections,[9] and also in chronic inflammatory infections where chronic immune stimulation is the norm.- Parvovirus B 19, Hepatitis B and C, Malaria, Leprosy, TB , and HIV AIDs[10]. When this happens, immune dysregulation, Hyperimmunity and Autoimmunity follows. A need for upregulating T Regs is therefore important.
We will show that Mammalian dsDNA which is methylated is non antigenic for human T cells (normal or SLE, PBMs) when measured by T cell blastogenesis in vitro. It suppresses T celll blastogenesis to memory antigens -(SK/SD): T and B cell mitogens-(PHA, CON A, and PWM); & Alloantigens in a dose dependent manner , which is abolished by prior DNAase treatment. This dsDNA effect is therefore antigen specific and dose dependent. The method of this suppression is the induction of suppressor/regulator T cells.[11] Mammalian DNA differs from bacterial DNA, which is antigenic *in vitro*,[13] and *in vivo*, due to it's CpG motifs , which are demethylated .[16] Antigenicity has been shown to be dependent, on TOLL receptor 9 activation, endosomal processing and antigen presentation to the TCR and BCR receptors and immune responses.[17] Mammalian dsDNA and inhibitory oligonucleotides (ODNs) block stimulatory ODNs at this endosomal site.[18] This is the first evidence however that mammalian dsDNA which is methylated is not only non antigenic, but tolerogenic *in vitro*, by activating suppressor/regulator Tcells.

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LONG TERM EFFECTS OF AN INTENSIVE TREATMENT USING RITUXIMAB IN SEVERE CASES OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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A proportion of SLE patients are refractory or intolerant to standard immunosuppression. These are candidate to new therapeutic options.
Eight patients, 6 women and 2 males, mean age 41 years (range 27-55 years), with severe multiorgan involvement including kidney, skin, central and peripheral nervous system, with polyarthritis, polysierositis, anti-phospholipid antibody syndrome were considered eligible for an intensive treatment using Rituximab. They were followed for 12-59 months.
Rituximab was administered intravenously at a dose of 375 mgm^2 on days # 2, 8, 15 and 22. Two more doses were administered 1 and 2 months later. This treatment was combined with two pulses of 750 mg cyclophosphamide (days # 4 and 17) and three intravenous pulses of 15 mg/kg (days # 1, 4 and 8) methylprednisolone followed by oral prednisone, 50 mg for 2 weeks rapidly tapered until 5 mg in two months without immunosuppressive maintenance therapy.
Levels of erythrocyte sedimentation rate and anti-dsDNA antibodies significantly decreased (p<0.01 at 12 months), whereas C3 and especially C4 values increased at 6 months (p<0.01 for C4). Proteinuria improved in all 5 cases presenting with renal involvement (p<0.01 at 3, 6 and 12 months). SLEDAI score ameliorated (mean 17.3) before and 3.1 after Rituximab treatment.
Long lasting remissions can be obtained in patients with severe SLE with major organ involvement, including kidney, by this intensive scheme using Rituximab followed by a rapid tapering of prednisone to 5 mg/day as a sole maintenance therapy.

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ELIMINATION OF AUTOREACTIVE B CELLS IN HUMANIZED SCID MICE MODELS OF SLE

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The pathological DNA-specific B cells in SLE are a logical target for a selected therapeutic intervention. It has been recently shown that complement receptor type 1 (CR1, CD35) on human B and T-lymphocytes has suppressive activity. The cocrosslinking of this receptor with BCR inhibits B cell activation and proliferation and it could be an attractive new target for negative signal delivery.
Experimental therapy in humans is limited by many restrictions. SCID mice, which lack both T and B lymphocytes and accept xenogenic cells have been used for human cell transfer for evaluating the pathogenesis of human SLE. We hypothesize that it may be possible to re-establish tolerance to native DNA in humanized SCID mice with cells from SLE patients by administering to them a chimeric molecule, containing a monoclonal antibody against the inhibitory human B-cell receptor CR1 coupled to a decapeptide DWEYSVWLSN that mimics antigenically DNA. This engineered molecule is expected to be bound selectively by the immunoglobulin receptors of B-cells with anti-native DNA specificity and to deliver selectively to them a strong suppressive signal.
Reconstituted SCID mice with PBMC from SLE patients showed presence of autoantibodies, as well as human immunoglobulin deposition in the renal glomeruli. Treatment of the transferred SCID mice with anti-human DNA-like chimeric molecules prevented appearance of IgG anti-DNA antibodies and proteinuria, while the PBS-injected animals had high levels after the cell transfer.
The presented transferred SCID model explores a novel approach for selective silencing of human autoreactive B cells and preventing pathological antibody responses.

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SIALYLATION OF INTRAVENOUS IMMUNOGLOBULINS DOES NOT IMPROVE EFFICACY IN A MOUSE MODEL OF AUTOIMMUNE THROMBOCYTOPENIA

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Introduction: Intravenous immunoglobulin (IVIg) is used to treat immune thrombocytopenia (ITP). It has been suggested that sialylation of the N-linked glycan present in the Fc part of the IVIg heavy chain is necessary for efficacy of IVIg therapy.
Objective: To examine the hypothesis that Fc sialylation is important for efficacy of IVIg in the amelioration of ITP.
Methods: We used a dose-escalation Balb/c mouse model of passive anti-platelet antibody (MWReg30)-induced ITP. Mice were injected with 68 µg/kg MWReg30 on days 0 and 1, followed by increasing doses of additional 34 µg/kg each subsequent day (cumulative) (Katsman et al.,*Transfusion*,50:1285, 2010). IVIg (1.0 g/kg) was given IP on day 2. Desialyation of IVIg (dsIVIg) was by treatment with neuraminidase and was confirmed by Lectin blot using biotinylated *Sambucus nigra* (SNA) lectin and/or by ELISA, as well as by glycan analysis using HPLC and mass spectrometry. Sialic acid-enriched IVIg was produced by affinity chromatography using SNA-lectin.
Results: MWReg30 caused platelet counts to fall to nadir within 48 hours and treatment with either IVIG or dsIVIG resulted in platelet counts increasing within 24 hours of administration and reaching similar maximal levels within 72 hours post administration. This result was reproduced in multiple experiments and was irrespective of the IVIg-manufacturer. Results using sialic acid-enriched IVIg did not show enhanced amelioration of ITP. Fc fragments from plasma derived IgG did not show sialic acid-dependent ability to ameliorate ITP.
Conclusion: Our results indicate that Fc sialylation of IVIg is not required for the amelioration of ITP.

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BAEKJEOLYUSIN-TANG AND BERBERINE BLOCK THE RELEASE OF COLLAGEN AND PROTEOGLYCAN FROM RABBIT CARTILAGE AND DOWN-REGULATE MATRIX METALLOPROTEINASES IN RABBIT CHONDROCYTES

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Osteoarthritis (OA) is a major degenerative disease affecting millions of individuals. The ability of articular cartilage to self-repair is limited due to a low tissue turnover rate and the avascular nature of the cartilage, making OA an irreversible disease. In Korea, however, many traditional Korean medical doctors have treated joint disease with a prescription of traditional Korean medicine, BaekJeolYuSintang (BYT). Thus, we investigated the chondroprotective effects of BYT and its active ingredient, berberine (Ber) in experimental model. Here we show that BYT or Ber significantly inhibits the expression of matrix metalloproteinase (MMP)-3 and a disintegrin and metalloproteinase with thrombospondin motifs-5 as well as increases the expression of tissue inhibitors of metalloproteinase-1, aggrecan, and collagen in rabbit articular chondrocytes (p<0.05). BYT or Ber significantly inhibits the secretion and activity of MMP-3 (p<0.05). In addition, BYT or Ber significantly inhibits the release of collagen and glycosaminoglycan into the culture media from rabbit articular cartilage explants (p<0.05). The data suggest that BYT or Ber has a therapeutic potential for the treatment of cartilage damage in osteoarthritis.

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SUCCESSFUL USAGE OF INTRARTICULAR ETANERCEPT FOR RESISTANT/RECURRENT MONOARTICULAR SYNOVITIS

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Introduction: While the usage of intra-articular(I/A) steroid injection is a well established therapy for inflammatory monoarthritis, it is not uncommon to encounter therapy resistant monoarthritis in clinical practice whereby joint synovitis recur despite systemic disease modifying drugs(DMARDs) and repeated I/A steroid injections. Etanercept is an anti-tumour necrosis factor(TNF) that is given subcutaneous to treat rheumatoid arthritis(RA). There are few reports concerning the usage of I/A etanercept injection.

Objective: To report a case series of Asian patients with recurrent inflammatory monoarthritis who were administered I/A etanercept and to present their outcomes, followed by a review of reported clinical experiences with I/A etanercept therapy.
Materials and methods: A consecutive series of 9 patients with recurrent inflammatory monoarthritis who had recurrent joint synovitis and effusion despite I/A steroids, I/A methotrexate were given a single or repeated dose of 25mg I/A etanercept and their clinical outcomes were reported.
Results: 8 patients had RA and 1 had seronegative arthritis with recurrent knee synovitis. All had been given DMARDs, oral steroids, NSAIDs, and 2 had therapy with S/C etanercept and 2 had IV Actemera(IL-6) biologic therapy. 8 had recurrent knee synovitis and 1 ankle synovitis. 8 out of 9 patients had improvement in their joint synovitis. No adverse effects were seen.
Conclusion: I/A etanercept is a useful adjunct therapy for those patients with recurrent joint synovitis who fail I/A steroid therapy and other systemic therapy. A brief review of previously published papers on I/A etanercept will also be presented and discussed.

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THE LINK BETWEEN MULTIPLE SCLEROSIS, T REGULATORY CELLS AND JAPANESE RICE

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The purpose of the present study was to develop a peptide for treatment of multiple sclerosis (MS). We have tested the effect of a novel antiinflammatory peptide (KGHYAERVG, termed IIIM1) on experimental autoimmune encephalitis (EAE), an animal model of MS. Our findings demonstrate significant reduction in neurological score following oral administration of IIIM1, as compared to the control groups received the vehicle (saline). Structural studies revealed that the entire peptide is required for activity. The peptide caused significant reduction in IL17, interferon gamma and IL12 production by isolated splenocytes and concomitant elevation of antiinflammatory cytokines. IIIM1 elevated T regulatory cells (Tregs, $CD4^+CD25^+FoxP3^+$) in brain and spleen of EAE mice. Similar proliferative effect was observed in isolated human and mouse Tregs *in vitro*. Stimulation of Tregs by IIIM1 caused production of a new peptide termed RA1 present in Oryza Sativa Japonica group. This Japanese rice peptide ameliorated neurological symptoms in the EAE model. Similar beneficial effect was observed upon oral administration of an extract of Japanese rice. In conclusion, oral treatment with IIIM1 ameliorates EAE symptoms via stimulation of Tregs to proliferate and produce RA1 which reduces EAE symptoms. These findings may explain the relatively low prevalence of MS in Japan and other Japanese rice-eating populations. (This work was supported in part by The Israel Science Foundation grant 747/05).

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BONE MARROW B-CELL CLONAL EXPANSION IN MIXED CRYOGLOBULINEMIA: ASSOCIATION WITH NEPHRITIS AND SWITCH INTO A POLYCLONAL PATTERN AFTER B-CELL DEPLETION

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Objectives: To investigate the relationship between the pattern of bone marrow (BM) B-cell expansion, the major clinical features of mixed cryoglobulinemia (MC) syndrome and the response to rituximab (RTX).
Patients and methods: Seventy-three patients with type II MC syndrome were analyzed. Median age was 63 years (range 24-82), there were 54 females and 19 males. Hepatitis C virus (HCV) was present in 56/73 patients (76.7%). Peripheral neuropathy was present in 49 (67.1%), nephritis in 16 (21.9%), skin ulcers in 16 (21.9%). Bone marrow (BM) B-cell expansion was evaluated by a seminested PCR amplification of the V-D-J region of the IgH genes. RTX therapy 375 mg/m^2 or 1 gram x 2 was administered in 43 patients.
Results: A clonal B-cell expansion was found in 42/73 (57.5%) patients. A pattern of clonal B-cell expansion increased the risk of nephritis of about 4 times (p=0.039, OR=4.184, $CI_{95\%}$[1.075;16.278]), if compared to a polyclonal pattern, confirming previous results. RTX was effective in 27/41 (65.8%) evaluable MC patients. A significant association was found between baseline clonal expansion and response to RTX (p=0.008, Chi square test). HCV infection was associated with response to RTX (p=0.002, OR=16.667, $CI_{95\%}$[2.790;99.565]). Among 16/43 patients treated with RTX, where BM expansion was re-evaluated after RTX therapy, change from clonal to polyclonal pattern was associated with response to RTX (p=0.026, Fisher's exact test).
Conclusion: Particular B cell clones are preferentially expanded in MC syndrome, in particular in MC nephritis, and may be targeted by RTX therapy, particularly in HCV positive patients.

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SERUM LEVELS OF RANKL, OPG AND TRAIL IN CHILDREN WITH POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH TNF INHIBITOR (ETANERCEPT)

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Biological treatment improves outcome of Juvenile Idiopathic Arthritis (JIA), an autoimmunological disorder characterized by a chronic inflammation of joints and by increased bone metabolism.
We investigated prospectively the serum levels of OPG, RANKL and TRAIL in 14 patients with polyarticular JIA qualified for the treatment with etanercept ,who were priorly treated unsuccessfully with DMARDs. The disease activity, TRAIL, OPG and RANKL levels were determined at baseline and 12 months after initiation of biological treatment. The level of RANKL was higher at baseline (0,24 pmol/l±0,35) and decreased after 1 year of a-TNF treatment (0,14 pmol/l±0,13). Serum OPG and TRAIL were lower at baseline (OPG 3,2 pmol/l±1,1 TRAIL 38,8pg/ml±18,9) and increased after 12 months (OPG 3,4 pmol/l±1,6 TRAIL 53,0 pg/ml±34,6). 8 patients did not achieve the remission after 12 months of a-TNF therapy. In this group RANKL level and RANKL/OPG ratio were higher at baseline than in patients who got the remission (RANKL 0,32 pmol/l±0,4 vs 0,11 pmol/l±0,08; RANKL/OPG 0,1±0,11 vs 0,03±0,04). TRAIL level at baseline was significantly lower in patients that achieved the remission (47,5 pg/ml±34,1) than in the remaining patients (79,1pg/ml±112). After 12 months of etanercept therapy TRAIL level increased in good responders (98,0 pg/ml±207,0) but decreased in poor responders (53,0 pg/ml±34,2).
The levels of TRAIL, RANKL and RANKL/OPG ratio may be helpful to determine the therapeutic response to a-TNF antagonists. The increase of TRAIL level and the decrease of RANKL level may indicate their prognostic value in severe form of JIA treated with etanercept.

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PHOSPHORUS-BASED DENDRIMER AS NANOTHERAPEUTICS TARGETING BOTH INFLAMMATION AND OSTEOCLASTOGENESIS IN EXPERIMENTAL ARTHRITIS

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Rheumatoid arthritis (RA) is an auto-immune inflammatory disorder characterized by inflammation of the synovial membrane, cartilage degradation and subsequent bone erosion by osteoclasts leading to joint deformation. Therapeutic approaches which have been developed since 15 years are immuno-biotherapies using mainly monoclonal antibodies and soluble receptors neutralizing the effects of cytokines involved in the initiation and development of RA or inactivating B and T cells. Although these biological drugs proved to be efficient, they are very expensive and they fail to cure RA and to inhibit or delay all its deleterious aspects. Thus, innovative chemical molecules that could prevent both the extensive production of pro-inflammatory cytokines and the enhanced differentiation and activity of osteoclasts might represent a real breakthrough in the treatment of RA. Phosphorus-containing dendrimers have been shown to display striking immunological properties towards immune cells. Among these dendrimers, azabisphosphonate-capped dendrimer, called ABP, selectively targets and activates human monocytes toward an anti-inflammatory pathway. Using the IL-1ra-/- mouse model, we have explored the potential of dendrimer ABP for the treatment of experimental arthritis. We have found that dendrimer ABP was efficient to resolve arthritis with a great improvement of synovial hyperplasia and cell infiltration in joints. Serum levels of pro-inflammatory cytokines were taken down to those of normal mice. This anti-inflammatory action was coupled to an anti-bone erosion activity mediated by c-Fms inhibition. Thus, this innovative molecule, which prevents both differentiation and activity of osteoclasts and enhanced production of pro-inflammatory cytokines, might be of great relevance in the treatment of RA.

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AUTOIMMUNITY IN PARENTS INCREASES THE OCCURRENCE OF ALLERGIC DISEASE IN THEIR OFFSPRING

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Introduction: Based on the Th1/Th2 paradigm, autoimmune disease and allergy, are thought to be mutually exclusive. These immune mediated diseases, however, are not only characterized by distinct pathogenic mechanisms but share common denominators as well (co-occurrence in patients, geographic distribution, rise in prevalence since 1950). Only an interaction between genetics and environment can explain the rapid rise in prevalence.
Methods: By means of a pilot study it was tested if any autoimmune disease in parents (rheumatoid arthritis or ankylosing spondylitis and/or psoriasis and/or diabetes mellitus type 1 and/or multiple sclerosis and/or colitis ulcerosa or Crohn's disease) increases the occurrence of any allergy in their offspring. A secondary research question was focused on the influence of the specific autoimmune diseases. The method used was based on epidemiologic population research with use of prospective academic general practice data, registered by the regional network of general practitioners (RNH, n=6328 families). A multiple logistic regression analysis was carried out.
Results: The results showed that any autoimmune disease in fathers (n=352), irrespective of co-occurrence of a diagnosis of allergic disease, increased the occurrence of any allergy in their children (n=1200, p=0.005, OR 1.503). Autoimmune rheumatoid diseases in the mothers (n=73, rheumatoid arthritis or ankylosing spondylitis, p=0.040, OR 1.722), and psoriasis in the fathers (n=193, p=0.036, OR 1.435), showed to be of main interest.
Discussion: As the power was insufficient and no environmental factors were included in the analyses, further research in larger samples, taking relevant environmental factors into account, will give more definite information.

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LUPUS NEPHRITIS, AN ACQUIRED ERROR OF CHROMATIN METABOLISM IN AUTOIMMUNE (NZBXNZW)F1 MICE

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Lupus nephritis is characterized by deposition of chromatin fragment-IgG complexes in the mesangial matrix and glomerular basement membranes (GBM). The latter defines end-stage disease.
In the present study we determined the impact of antibodies to dsDNA, renal Dnase1 and matrix metalloprotease (MMP) mRNA levels and enzyme activities on early and late events in murine lupus nephritis. The major focus was to analyse if these factors were interrelated, and if changes in their expression explain basic processes accounting for lupus nephritis.
Early phases of nephritis were associated with chromatin-IgG complex deposition in the mesangial matrix. A striking observation was that this event correlated with appearance of anti-dsDNA antibodies and mild or clinically silent nephritis. These events preceded down-regulation of renal Dnase1. Later, renal Dnase1 mRNA level and enzyme activity were reduced, while MMP2 mRNA levels and enzyme activity increased. Reduced levels of renal Dnase1 were associated in time with deficient fragmentation of chromatin from dead cells. Large fragments were retained and accumulated in GBM. Also, since chromatin fragments are prone to stimulate Toll-like receptors in e.g. dendritic cells, this may in fact explain increased expression of MMPs. These scenarios may explain the basis for deposition of chromatin-IgG complexes in glomeruli in early and late stages of nephritis, loss of glomerular integrity and finally renal failure.
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GENE POLYMORPHISMS OF TNF-ALPHA AND IL-10 RELATED TO RHEUMATIC HEART DISEASE

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Background: Rheumatic fever (RF) is inherited as a single recessive gene. Several genes are Likely to predispose an individual to develop rheumatic fever and rheumatic heart disease(RHD). Polymorphisms of TNF-α gene were associated with susceptibility to develop RF, IL-10 expression was characterized in heart tissue of RHD patients by immuno-histochemistry.
Aim: To test the relation of RHD and gene polymorphisms of pro-inflammatory cytokines TNF-α gene at position -308 and anti -inflammatory IL-10 gene at position -1082.
Patients and methods: 20 children with chronic rheumatic heart disease and 10 healthy children as a control group. Patients group was classified into patients with single, and multiple valvular lesions, They were classified according to the severity by Echocardiography into:
Group I: mild valvular lesion, Group II: moderate lesion, Group III: severe Lesion.
Real time PCR was done for both TNF-α at-308 and IL-10 at position - 1082.
Results: All cases showed significant higher frequency of TNF-α homozygous genotype G/G compared to control group. Cases with severe valvular lesions showed increased frequency of homozygous genotype G/G and increased frequency of IL-10 genotype G/A in cases. Composite genotypes (TNF-α G/G,IL-10 G/A) were higher in cases compared to control group, while composite genotypes (TNF-α G/A,IL -10 G/G) were higher in control group.
Conclusions: RHD is associated with cytokine gene polymorphisms of TNF-α homozygous genotype G/G at-308 and IL-10 G/A at 1082 , genotypes (TNF-α G/G,IL-10 G/A) had high risk for RHD, (TNF-α G/A,IL-10 G/G) may be protective.

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NZB/WF1 MICE DEVELOPED ASIA SYNDROME WHEN INJECTED WITH COMPLETE FREUND'S ADJUVANT

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Objectives: We investigated the effects of Complete Freund's Adjuvant (CFA) injections on survival of NZB/WF1 mice.
Methods: Twenty female NZB/WF1 mice of 8 weeks were subdivided in two groups: 10 treated with 100 ml s.c. injections of CFA + 100 ml 1xPBS and 10 with 200 ml s.c. injections of PBS, as controls. Mice were treated at 10th, 13th and 16th weeks of age. Urine was collected weekly and proteinuria was measured. Anti-dsDNA antibodies were assessed during the treatment. Histological abnormalities were evaluated. Survival was analysed by Kaplan-Meier method using Mantel-Cox test for comparisons.
Results: The survival curve was significantly reduced in CFA injected mice compared with those treated with PBS (p=0.002). At the age of 25 weeks, all CFA treated mice were died vs 40% of those injected with PBS (p=0.002).
Mean proteinuria levels (mg/dl ±SD) were higher in CFA injected mice compared with those treated with PBS: week 13th 15±14.14 vs 0, p=0.005; week 16th 43.50±90.95 vs 6±7.75, p=0.042; week 21st 720±383.41 vs 50.63±41.36, p=0,003.
Anti-dsDNA antibody levels (OD ±SD) were higher in CFA treated mice than in those treated with PBS: 13th week 0.42± 0.16 vs 0.16± 0.08, p=0.001; week 16th 0.57±0.24 vs 0.28±0.24, p=0.041. CFA treated mice showed more significant renal damage than those PBS injected.
Conclusions: CFA injections reduce the survival of NZB/WF1 mice by stimulating immune system and worsening glomerulonephritis. Our results suggest that CFA should be avoided as adjuvant during immunization of autoimmune prone mice in experimental studies.

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B AND T CELL INFILTRATE IN SCLERODERMA SKIN: B CELLS CHARACTERIZE MAINLY EARLY AND DIFFUSE SYSTEMIC SCLEROSIS

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Introduction: The dermal cellular infiltrate in systemic sclerosis(SSc) has not been completely defined. The purpose of this study was to characterize the frequency and the distribution of B and T cells in scleroderma skin according to the disease duration and clinical characteristics.
Methods: Twenty-eight SSc patients underwent skin biopsies on clinically involved skin(distal forearm) and on clinically uninvolved skin(buttock). Immunohistochemistry was carried out on paraffin sections using anti-CD3 and anti-CD20 mouse monoclonal antibodies to identify T and B cells, respectively.
Results: CD20-positive cells were found in 17 (60.7%) patients: 9 (52.9%) of these presented CD20-positive cells on the forearm and on the buttock, 7 (41.2%) only in involved skin. All patients with CD20-positive cells on clinically uninvolved skin had a diffuse disease. The mean number of CD20-positive cells was higher in involved skin (4.7±5.9) with respect to uninvolved skin (1.9±2.9) (p=0.04) and patients with early SSc had a greater number of CD20-positive cells (6.3±6.5) with respect to patients with long-standing disease (1.2±0.9) (p=0.009). All specimens showed CD3-positive cell infiltrate predominantly in a perivascular location in the mid and deeper portion of the dermis. The mean number of CD3-positive cells was higher in clinically involved skin (71.7±34.6) with respect to clinically uninvolved skin (45.7±36.0) (p=0.001).
Conclusions: These results confirm that T cells are present in all SSc patients, while B cells seem to characterize patients with early disease and diffuse skin involvement. Moreover, our data suggest a possible role of these cells, above all during the first phases of the disease.

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RF AND SERUM PAD4 IN LUNG CANCER IS NOT ASSOCIATED WITH ANTI CCP ANTIBODY PRODUCTION

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Rheumatoid arthritis is characterized by anti-citrullinated protein antibodies (ACPAs), produced against citrullinated proteins. In the pathogenesis of the disease the interaction of environment and genetics have a role as smoking is an important risk factor for the development of ACPA positive RA. However, the link among smoking, citrullination, catalyzed by peptidyl arginine deiminases (PADs), and ACPAs has not yet been elucidated. Thus, we searched for a model without polyarthritis where there is increased cell death allowing the formation of autoantibodies. We proposed that lung cancer might be a good candidate supported by the following considerations: smoking plays a role in its pathogenesis; the disease is often accompanied by paraneoplastic syndrome; smoking increases citrullination in the lung; several malignant tumor tissues are associated with increased citrullination; RA synovium and lung cancer tissue have similarities.Serum PAD4, rheumatoid factor (RF) and ACPA levels were measured in 42 lung cancer patients and 67 non-tumorous pulmonary patients and healthy controls. All parameters were compared according to smoking history.None of the patients had polyarthritis or autoimmune disease. Abnormal PAD4 and RF levels were frequently found in smoker lung cancer patients, compared to non-smokers. Two out of 30 smoker lung cancer patients had high anti-CCP levels. Smoking intensity was significantly higher among smoker lung cancer patients, compared to healthy smokers, however, did not correlate to the measured serum parameters.In conclusion, smoking might influence PAD4 levels and RF production. High serum PAD4 and RF levels together with smoking are not sufficient for the formation of ACPAs and autoimmunity.

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ARTHRITIS AND AGEING: SIMILARITIES AND DIFFERENCES IN CD28-ASSOCIATED GENE USAGE BY HEALTHY ELDERLY AND RHEUMATOID ARTHRITIS PATIENTS´ $CD4^+$ LYMPHOCYTES

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One of similarities between the behavior of $CD4^+$ lymphocytes during physiological ageing and rheumatoid arthritis (RA) is reduced expression of CD28 culminating in increased proportion of $CD4^+CD28^{null}$ lymphocytes. We have asked if homologues of a DNA sequence ('alpha') present in the CD28 promoter and apparently involved in the downregulation of CD28 expression are also present in the promoter or regulatory regions of other genes important for $CD4^+$ cell function. We have found four 'alpha'-containing genes expressed in human $CD4^+$ cells: ZNF334, KLOTHO, RARβ2 and GRAP2. Interestingly, the changes of expression pattern when RA individuals are compared to healthy controls, especially if individual age is taken into consideration, are unique for each of the four genes. So, except of GRAP2 showing no relation to disease or individual age, these genes' expression is significantly more suppressed in the cells of RA patients than in those derived from healthy controls. However, for the gene expression regulator ZNF334 this suppression in the patients' lymphocytes occurs regardless their age, making the gene a possible disease marker; it does not change significantly during healthy ageing. Expression of the 'ageing hormone' KLOTHO and of retinoic acid receptor RARβ2 is reduced proportionally to individual age, but this reduction occurs at younger age and is more pronounced for the lymphocytes of RA patients. Concluding, our observations confirm the hypothesis of earlier ageing of RA patients' $CD4^+$ cells, but show that not every gene (even if supposedly undergoing common regulation) behaves similarly in the RA and healthy elderly lymphocytes.

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IMBALANCE OF EFFECTOR AND REGULATORY T CELL SUBSETS IN PATIENTS WITH SJÖGREN'S SYNDROME

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The abnormal interaction between effector and regulatory T cells (Treg) is a hallmark of autoimmune systemic diseases and is known that both loss of self tolerance and predominance of autoreactive clones and proinflammatory cytokines may contribute to disease development. We demonstrated an expansion of a $CD4^+CD25^-$ $FoxP3^+$ T-cell population, expressing high levels of GITR and displaying in vitro suppressive activity, in patients with primary Sjögren's syndrome (SS) compared to normal controls (NC). In parallel, a reduction of conventional $CD25^{high}FoxP3^+$ Treg cells has been also shown. The effector T lymphocytes targeted by Treg cell are mainly Th1 but, following the recent identification of the $CD4^+$Th17 cell population, a reciprocal interaction between Th17 and Treg cells has been found. Moreover, it has been recently demonstrated that a small $CD3^+$ T cell population lacking of both CD4 and CD8 is able to produce IL-17 *in vitro*. This cell subset, known as $CD4^-CD8^-$ double negative (DN), is known to be expanded in the peripheral blood of patients with systemic lupus erythematosus and to accumulate in the kidney during lupus nephritis. We found that total circulating DN T cells are significantly expanded also in SS compared to NC and that SS freshly isolated DN T cells produce larger amounts of IL-17 with respect to NC. According to our data, unconventional Treg cell subsets may be expanded as a compensatory mechanism to restore conventional Treg cell impairment and counteract effector T cells. Therapeutic agents targeting this cell subset may represent an innovative approach in clinical practice.

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DIAGNOSIS OF MILD MEVALONATE KINASE DEFICIENCY IN ADULTS BY INDIRECT GENETIC TECHNIQUES

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Aims: Mevalonate Kinase Deficiency (MKD) is a recessive autoinflammatory disorder characterized by recurrent fever and musculoskeletal manifestations. MKD is due to mutations in *mvk* which cause variable degrees of enzyme deficiency.Genetic investigation is essential for the diagnosis, especially in patient with normal IgD values.Determination of mutations in patients with suspicion of MKD can be more efficient using indirect techniques.
Methods: Starting from 2007 we evaluated 43 patients (mean age 29 years, range 18 - 61 years) affected by recurrent fevers and other clinical manifestations usually found in autoinflammatory syndromes and not correlated with infections or autoimmune diseases. IgD level was measured in all patients.
Molecular testing was performed in DNA extracted from PBMC. The gene *mvk* was analysed by means of DHPLC and automatic sequencer ABI PRISM 3130 Genetic Analyzer (APPLIED BIOSYSTEMS). Primers for PCR amplifications were designed in our laboratory.
Results: There was no relationship between high levels of serum IgD and the presence of sequence alterations in MVK. 31 out of 43 patients examined had at least one altered DHPLC profile. Data were confirmed by sequencing. The number of SNPs per patient was greater in the group of patients with MKD-typical fever than MKD-atypical (p=0.0023).
Conclusions: A high level of serum IgD is no longer a marker for diagnosis of MKD. Genetic analysis is crucial in patients with suspected MKD and normal IgD. The great number of SNPs in *mvk* per patient may induce a decrease in the activity of MK, inducing a mild MKD.

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ANTI-APOLIPOPROTEIN A-1 AUTOANTIBODIES ARE ACTIVE MEDIATORS OF ATHEROSCLEROTIC PLAQUE VULNERABILITY

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Introduction: Our recent work indicates that anti-apolipoprotein A-1 (apoA-1) IgG is an independent predictor of poor cardiovascular outcome in Rheumatoid Arthritis (RA) and Myocardial Infarction patients with an intimate relationship to inflammation and basal heart rate regulation, two major determinants of cardiovascular outcome. The potential relationship between anti-ApoA-1 IgG and plaque vulnerability remains elusive.
Objectives: To investigate the role of anti-ApoA-1 IgG in plaque vulnerability both in humans and apoE knock-out (-/-) mice.
Methods: Potential relationship between anti-ApoA-1 IgG and features of cardiovascular vulnerability was explored both *in vivo* and *in vitro*. *In vivo*, we investigated anti-apoA-1 IgG in patients with severe carotid stenosis (n=102) and in ApoE-/- mice infused with polyclonal anti-apoA-1 IgG. *In vitro*, anti-ApoA-1 IgG effects were assessed on human primary macrophages, monocytes and neutrophils.
Results: Intraplaque collagen was decreased, while neutrophil and MMP-9 content was increased in anti-apoA-1 IgG positive patients and anti-ApoA-1 IgG-treated mice as compared to corresponding controls. In humans, serum anti-apoA-1 IgG levels positively correlated with intraplaque macrophage, neutrophil and MMP-9 content, and inversely with collagen. *In vitro*, anti-apoA-1 IgG increased macrophage release of CCL2, CXCL8 and MMP-9, as well as neutrophil migration towards TNF-α or CXCL8.
Conclusions: These results suggest that anti-apoA-1 IgG might be considered as active factors that directly increase atherosclerotic plaque vulnerability in humans and mice. Whether this could account for the increased rate of cardiovascular complications observed in RA patients with high titres of anti-apoA-1 IgG remains to be demonstrated.

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FREQUENCY OF TH17 CD20+ CELLS IN THE BLOOD OF RHEUMATOID ARTHRITIS PATIENTS IS HIGHER COMPARED TO HEALTHY CONTROL SUBJECTS

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Objectives: Anti-CD20 biologics can deplete B cells from patients with autoimmune and proliferative disorders. Some autoimmune diseases are T cell driven and the ability of B cell depleting biologics to alleviate autoimmune disease is not fully understood. The present study examined the proportion of CD20+ T lymphocytes in the peripheral blood of healthy control subjects (HC) and peripheral blood and synovial fluid (SF) of rheumatoid arthritis (RA) patients and determined if CD20+ T cells belong to the Th17 subset implicated in the development of RA.
Methods: The phenotype (CD3 and CD19) and apoptosis status of lymphocytes were examined by flow cytometry. IL-17 status and secretion was determined using a commercial IL-17 detection assay. Apoptosis and necrosis was assessed by double staining of cells for annexin V and 7-aminoactinmyocin D respectively.
Results: In the peripheral blood of HC and RA patients, the median percentage (interquartile range) of total lymphocytes that expressed CD20+ was 8.9 % (3.4-12.6) and 10.3 % (4.2 -26.7) respectively and comprised predominantly of B cells (approximately 85%). Approximately 4% of CD3+ T cells from both HC and RA individuals co-expressed CD20. In the blood of HC <0.1% of CD20+ T lymphocytes were capable of secreting IL-17. In contrast, 24.2% of CD20+ T lymphocytes in RA blood secreted IL-17 (240-fold increase; p=0.02).
Conclusions: These findings demonstrate that Th17 CD20+ cells are present in significantly greater amounts in the peripheral blood of RA patients compared to healthy individuals and may be an additional target for anti-CD20 therapies.

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PATHOGENIC POTENTIAL OF THE POSTTRANSLATIONALLY MODIFIED HUMAN IMMUNOGLOBULINS CLASS G AND M

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Background and aims: Redox-reactive antibodies gained a wide area of interest after their autoimmune reactivity was discovered following treatment with chemical and physiological oxidants. The aim of study was to evaluate the pathogenic potential of oxidatively modified antibodies by assessing their binding to autoantigens and to determine their effects on human endothelial cells (HUVEC).
Methods: Aliquots of IgGs and IgMs, purified from healthy donors'sera, were electrochemically oxidized and analyzed for alterations in immunoreactivity by ELISAs and immunofluorescence. Proinflammatory effects were tested on HUVEC, posttranslational modifications were investigated by 2,4-dinitrophenylhydrazine reaction.
Results: Oxidized IgG fractions bound to β2-glycoprotein I and cardiolipin in low or medium titers, to cyclic-citrullinated peptide, proteinase 3 and cell antigens (atypical c-ANCA; non-specific cytoplasmic pattern in HEp-2 test). Oxidized IgG fractions induced morphology changes in HUVEC along with 2 and 4-fold increase in IL-6 in mRNA and protein level, respectively. Furthermore, increased immunoreactivity to β2-glycoprotein and cardiolipin was observed in all tested oxidized IgMs. In oxidized IgG and IgM fractions 2.5 or 5-fold increase in the protein carbonyl content was determined compared to non-oxidized controls.
Conclusions: Results suggest a direct involvement of redox reactions in the surface topology modifications of antibodies, resulting in their increased autoreactivity. An increase in the carbonyl moiety points toward a potential modification of amino acid side chains in oxidized antibodies. Detected binding in *in vitro* diagnostic tests and observed potency on endothelial cells support pathogenic reactivity of oxidized antibodies and reveal the importance of individual's redox status in maintenance of autoimmune reactions.

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TWO FACES OF CD4+ T CELLS IN RHEUMATOID ARTHRITIS – ACTIVATION OR SUPPRESSION?

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Rheumatoid arthritis (RA) is a chronic autoimmune disease with unknown etiology, but huge immune system involvement is postulated and researched. The major effort in immunological studies is focused on RA synovial membrane; changes of peripheral blood $CD4^+$ T cells in RA are less studied, especially in a context of disease activity and onset age. Therefore we decided to study phenotype and function of peripheral blood $CD4^+$ T cells in RA patients, regarding chronological and onset age, and disease activity.
Seventy RA patients and 30 healthy people were included into the study. Disease activity was measured by DAS28; expression of activation markers CD25, CD69, HLA-DR and CD95 and of CD28 was measured by flow cytometry on peripheral blood $CD4^+$ lymphocytes. The proliferative dynamics of $CD4^+CD28^+$ cells was studied by cytometric DCT method, and relevant kinetic parameters of cell cycle were compared.
Increased proportions of activated $CD4^+CD69^+$, $CD4^+CD25^+$, $CD4^+HLA\text{-}DR^+$, and $CD4^+CD95^+$ cells in RA patients were associated with higher disease activity, older chronological age and age of onset. Proportion of $CD4^+CD28^-$ cells increased in RA patients proportionally to higher DAS28.
Proliferating $CD4^+CD28^+$ lymphocytes from RA patients exhibited longer G_0-G_1 phase, shorter cell cycle, fewer cells entering the cycle and more apoptosis then control cells.
Concluding, peripheral $CD4^+$ T cells from RA patients show increased activation phenotypes alongside with higher disease activity and in relation to onset age, but on the other hand show signs of skewed, less vigorous and less productive proliferation in vitro, thus showing two significantly different faces.

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VERY EARLY RHEUMATOID ARTHRITIS (VERA) IS THE MAJOR PREDICTOR OF MAJOR OUTCOMES: CLINICAL ACR REMISSION AND RADIOGRAPHIC NON-PROGRESSION

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Objectives: Very early rheumatoid arthritis(VERA) is the definition of a clinical entity needing a real place in terms of patient stratification and outcome. We addressed the issue of whether a VERA could be the best predictor in terms of clinical remission as well as no x-ray progression in a cohort of ERA treated with a strict protocol.
Methods: 121 patients with ERA were treated to reach clinical remission with Methotrexate for three months, then a combination with subcutaneous anti-TNF was begun if the patient had not achieved a DAS≤2.4. At time 0 and after twelve months all the patients performed hand and foot joint radiographs, that were scored for the erosion score.
Results: 46.3% of the patients reached DAS remission and 24.8% achieved ACR remission. More than 70% of patients reached remission in monotherapy withmethotrexate. Male sex and an ESR < 35 mm/h at onset arose as significant predictors of EULAR remission, while a VERA disease resulted the only predictor of ACR remission.
At baseline 28.1% of the patients were erosive. Multivariate analysis demonstrated that the only independent predictor of erosiveness already at baseline was "not having a VERA disease". After 12 months, despite a tight control therapy approach, 14 patients became erosive and 13 patients presented a worsening of erosion score.
Conclusions: Our study suggests that VERA represents the best therapeutic opportunity in clinical practice to achieve a complete remission and to stop the erosive course of RA. An aggressive protocol cannot allow to completely avoid the radiological progression damage.

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COMPLEMENT SYSTEM IN RHEUMATOID ARTHRITIS: EVIDENCE OF CORRELATION WITH DISEASE ACTIVITY BUT NOT WITH ANTI-CITRULLINATED PROTEIN ANTIBODIES

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Objectives: Anti-citrullinated protein antibodies (ACPA) are a hallmark of rheumatoid arthritis (RA). Complement system has been found consumed and activated in synovial fluid from RA patients and appeared to correlate with disease activity. We investigated the role of ACPA on complement system in RA patients, and whether anti-TNF agents could possibly modify ACPA and/or complement levels.
Methods: One-hundred fourteen RA patients (89F/25M) diagnosed according to 1987 ACR criteria were enrolled. ACPA were detected by ELISA and considered positive at >20U/ml. Complement fragments C3 and C4, total hemolytic activity (CH50), ESR and CRP were measured. Disease activity was measured with the DAS28 score. Seventy-eight patients were treated with TNF antagonist and were studied also after 22 weeks of therapy.
Results: Seventy-eight patients were ACPA positive (ACPA+) while 36 patients were ACPA negative (ACPA-). No significant differences in complement levels between ACPA+ and ACPA- patients were observed. No correlation was observed between ACPA levels and complement C3, C4 and CH50 levels when Spearman´s test was performed. Disease activity was similar in ACPA+ and ACPA patients (DAS28 4.85 vs 4.47) and significantly ameliorated after 22 weeks of anti-TNF therapy showing a moderate EULAR response. A positive correlation was found between complement C3 and C4 and DAS28 score.
Conclusions: Although ACPA were found capable to activate complement via both the classical and alternative pathways, complement C3, C4 and CH50 levels detected in vivo in RA patients´ sera seem independent from ACPA, but may prove useful to monitor disease activity in anti-TNF treated patients.

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RISK FACTORS FOR RHEUMATOID ARTHRITIS MORTALITY: FUNCTIONAL DISABILITY AND COMORBIDITY ARE MORE SIGNIFICANT THAN LABORATORY TESTS AND RADIOGRAPHIC SCORES

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Objective: To analyze risk factors for premature mortality in RA in 53 reported cohorts, and in 210 patients.
Methods: Published risk factors in 53 cohorts, and in 210 patients 5-20 years after baseline in 1985, were reviewed. Significance was analyzed by univariate and multivariate Cox regressions.
Results: In 53 publications, significance in multivariate analyses for physical function was reported in 72%, comorbidity 65%, rheumatoid factor 45%, extra-articular disease 44% ESR 37%, socioeconomic status 31%, joint count 22%, radiographic score 11% of cohorts. In univariate analyses of the 210-patient cohort, age, years of education, physical function, and comorbidity, were significant 5,10,15 and 20 years after baseline, male gender and swollen joint count at later times, radiographic scores only at 15 years, and tender joint count, pain score, and rheumatoid factor not at any time. In multivariate Cox regression models, comorbidity was always significant, age and MDHAQ physical function at 5 and 10 years, ESR at 5 years, male gender at 10, 15 and 20 years, and swollen joint count at 15 and 20 years.
Conclusions: Physical function and comorbidity are more significant as risk factors for premature mortality in RA than radiographic scores and laboratory tests.

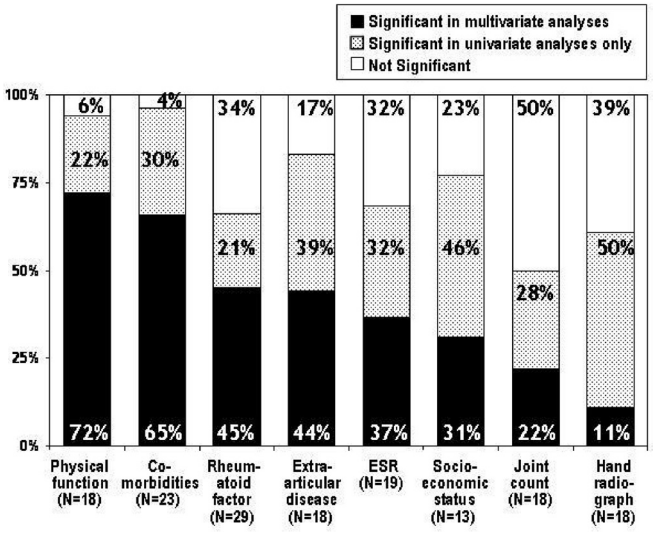

Figure. Significance of 8 variables to predict mortality in RA in 53 cohorts. X-axis. variable (number of reports in which variable was assessed). Y-axis. percentage of reports in which variable was significant in multivariate analyses (black), in univariate analyses only (grey), and not significant (white).

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CARDIOVASCULAR EVENTS IN A HIGH RISK MEDICAID POPULATION WITH RHEUMATOID ARTHRITIS

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Background and aims: Patients with Rheumatoid Arthritis (RA) experience excess cardiovascular (CVD) morbidity and mortality. RA doubles the risk for myocardial infarction (MI) and stroke; younger patients being at higher risk. We investigate the impact of RA on CVD morbidity in a high risk Medicaid managed care population, largely female, African American, young adults, with baseline CVD risk factors of hypertension and diabetes.
Methods: Maryland Medicaid claims data for patients with diabetes and/or hypertension, from January 2001-June 2006 were analyzed. Using exploratory analysis, we assessed the prevalence of RA and of CVD, as well as the prevalence of CVD within the RA population. Logistic regression analysis was used to explore the joint impact of RA, demographics, hypertension and diabetes on the likelihood of having a CVD event.
Results: The prevalence RA was 2.2% among patients at high-risk for CVD. Patients with RA were significantly older (mean age 49 vs. 34, $p<0.0001$), largely females (80% vs. 64%, $p<0.0001$) and non-African American (55% vs. 59%, $p<0.0001$) than those without RA. CVD prevalence was significantly higher in the RA population among compared to the general population (37% vs. 17%). After adjusting for demographics (age, gender, race) and risk factors (hypertension, diabetes), RA significantly increased the likelihood of CVD events (OR: 1.539, 95% CI: 1.416-1.674). In the adjusted model, hypertension (OR: 3.227) and diabetes (OR: 2.035) also independently increased the likelihood of CVD events.
Conclusion: We found that RA independently increased cardiovascular risk, 1.5 times, in a Medicaid population with high baseline risk.

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LOW-DENSITY LIPOPROTEIN METABOLISM IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Introduction: The increased prevalence of premature atherosclerosis in rheumatoid arthritis (RA) is well established. The lipid profile in this disease is controversial. Some alterations in low-density lipoprotein (LDL) metabolism may be not observed in the LDL cholesterol concentrations.
Objective: The objective of this study is to evaluate the LDL metabolism in patients with RA. For this purpose, the LDE cholesterol-rich nanoemulsion plasma removal, that mimics LDL, was evaluated.
Methods: LDE plasma kinetic was evaluated in 19 patients with RA and in 10 healthy subjects. LDE nanoemulsion labeled with ^{14}C-cholesteryl ester (^{14}C-CE) and ^{3}H-cholesterol (^{3}H-C) was injected intravenously. After injection, blood samples were collected in pre-determined intervals (5 minutes, 1, 2, 4, 6, 8 e 24 hours) and the radioactivity was counted by scintillation. Plasma decay curves were traced and it was calculated their fractional clearance rate (FCR) by compartmental analysis.
Results: The RA and healthy (H) groups do not differ in FCR-CE (h^{-1}) (RA: 0.0842±0.0679; H: 0.0497±0.0280, p=0.1386), FCR-C (h^{-1}) (RA: 0.0737±0.0474; H: 0.0512±0.0554, p=0.6552), total cholesterol (mg/dL) (RA: 206±42; H: 184±25, p=0.1393), HDL-C (mg/dL) (RA: 63±17; H: 50±6, p=0.0538), LDL-C (mg/dL) (RA: 121±35; H: 110±21, p=0.3555) triglycerides (mg/dL) (RA: 113±57; H: 118±72, p=0.8368), glucose (mg/dL) (RA: 88±15; H: 83±12, p=0.3563).
Conclusion: The FCR-CE indicates the plasma removal rate of LDE particle and FCR-C also indicates the transfer of unesterified cholesterol. These data show that there is no difference between RA and control groups. Therefore, the data suggests that RA does not impair the plasma kinetics of LDL.

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EARLY IMPAIRMENT OF CORONARY MICROCIRCULATION AND ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is characterized by an increase in cardiovascular (CV) mortality compared to the general population. Endothelial dysfunction begins early after the onset of the disease and play a pathogenetic role in the development of atherosclerosis. Our goal was to evaluate the relationship between coronary flow reserve (CFR), common carotid intima-media thickness (IMT) and asymmetric dimethylarginine (ADMA) in RA patients.
Methods: 120 adult patients with RA fulfilled ACR criteria [M 20 (16.6%), F 100 (83.4%), mean age 61±13 years] without clinical evidence of CV disease underwent dypiridamole stress echo evaluated CFR in the left descending coronary artery. Common carotid IMT was studied by carotid ultrasound and plasma ADMA levels were measured.
Results: 72/120 patients (60%) had CFR<2.5 of which 14/120 (12%) had CFR<2. All patients had normal wall motion at rest and during stress. Common carotid IMT was in normal range (0.73±0.13 mm) while plasma ADMA levels were increased (0.72±0.10). Linear regression analysis showed a significant negative correlation between CFR and common carotid IMT ($p<0.001$), plasma ADMA levels ($p<0.001$) and patient's age (p=0.019). Moreover, CFR resulted negatively related with rheumatoid factor levels (p=0.0009) and visual analogue score (VAS) (p=0.0092).
Conclusions: RA patients without clinical evidence of CV diseases showed an early impairment of endothelial dysfunction before structural changes of large vessels occur. This suggests that reduced CFR is an early marker of enhanced atherosclerosis in a preclinical stage and it is associated with endothelial dysfunction. Moreover, indexes of disease activity resulted negatively associated with coronary microcirculation function.

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ADALIMUMAB CORRECTS LONG-TERM ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS

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Endothelial dysfunction (ED), with an impaired endothelium-dependent vasodilation (FMD), is the vascular expression of systemic inflammation in rheumatoid arthritis (RA) and is a marker of an increased cardiovascular risk, potentially reverted by the anti-TNF-α agents. We studied the long-term endothelial effects of anti-TNF-α drugs in 25 patients (23 females, 2 males, aged 58.7±14.3 years), assessing the FMD by high-resolution ultrasound of the brachial artery, at baseline, after 1, 2, 6 weeks and then every 6 months of treatment with infliximab (8 pts), etanercept (10pts) or adalimumab (10 pts).The FMD significantly improved at 6 weeks (from 4.6±4.1 to 13.5±6.0, $p<0.05$) and at two years (12.4±7.3 vs 4.6±4.1, $p<0.05$), with a complete clinical remission. The anti-TNF-α drugs were withdrawn for a loss of response or various adverse effects in five patients treated with infliximab and two with etanercept; the FMD worsened before the loss of response but improved after the shift to adalimumab. Currently, a persistent clinical and endothelial response is recorded in 25% of infliximab patients at 4 years, 60% of etanercept patients at 5 years and 100% of adalimumab pts at 2 years ($\chi 2=11.013$, $p<0.01$). Our results confirm the high prevalence of ED in RA and its reversibility by selective antagonism of TNF-α, with an overt coherence with the clinical response. In our experience, the humanized anti-TNF-α antagonist seems to be the most effective in maintaining a persistent endothelial and synovial response.

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USEFULNESS OF POWER DOPPLER TO PREDICT RADIOLOGICAL DAMAGE IN RHEUMATOID ARTHRITIS PATIENTS IN CLINICAL REMISSION BY TNF-ALPHA BLOCKERS

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Introduction: Functional outcome of patients with rheumatoid arthritis (RA) depends from disease activity and radiological damage. Remission can be achieved in the majority of RA patients. Recent imaging studies identified subclinical inflammation in many patients with DMARDs considered in remission: Power Doppler (PD) correlated best with further radiological progression. TNF-α blockers are more efficacious in blocking radiological damage. It is not known if PD predicts on-going damage in RA patients in remission by TNF-α blockers.
Methods: Prospective observational study was performed on 109 consecutive RA patients in therapy with TNFα blockers. Patients in DAS28 remission since 6 months were considered. At baseline ultrasound examination was performed. Semi-quantitative PD scoring 0-3 was assessed. Radiological progression was expressed as difference in total Sharp Score >0 on x-rays at baseline and after one year. Correlations between PD and radiological progression were analyzed.
Results: Of 109 patients 54 showed no PD signal, whereas 55 had PD signal: 31 grade 1, 15 grade 2 and 9 grade 3. All patients without PD signal didn't show radiological progression. Radiological progression occurred in 29,1% of patients with PD and 14,68% of all patients analyzed. Radiological progression correlated with PD scoring grades: 22,6% of patients with grade 1, 40% with grade 2 and 50% with grade 3.
Conclusions: PD demonstrated to be useful in evaluating patients in remission with TNF-α blockers. Absence of PD guarantees arrest of radiological progression, whereas patients with PD signal are at risk of radiological progression. This risk increases with higher PD grades.

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THE ANTERIOR CHEST WALL IN SPONDYLOARTHRITIS: AN UNDERESTIMATED INVOLVEMENT

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Background: The anterior chest wall (ACW) is frequently affected in spondylarthritis (SpA), although its involvement is underestimated. Plain radiography appears of limited value, bone scintigraphy (BS) seems to have high sensitivity but low specificity. Magnetic resonance (MRI), appear more effective to study the initially changes found in early SpA (≤1 year).
Objectives: Aim of this study was to compare the reliability of BS and MRI, in assessing the involvement of ACW in patients with early SpA.
Methods: Out of 105 consecutive patients (pts) with early SpA, 31 (29.5%) complained of symptoms in the ACW and were submitted to BS and targeted MRI.
Results: At clinical examination, the right sternocostoclavicular (SCCJ) was involved in 28 pts (90.3%), the left SCCJ in 25 pts (80.7 %) and the sternum in 4 pts (12.9%). BS was positive in 26 pts (83.8%) and MRI in 18 pts (58.1%). At BS, the most frequently involved joints were the left and right SCCJ, respectively in 16 pts (51.6%); and in 19 pts (61.2%), followed by the sternum, found in 12 pts (38.7 %). MRI too showed a more frequent involvement of SCCJ, found in 17 pts (54.8%), followed by the sternum in 6 pts (19.4%).
Conclusions: The ACW involvement in early SpA is not are and both two imaging methods seem useful for evaluation. The BS confirms its higher sensitivity and, although less specific, it can reveal a subclinical involvement. MRI may give information useful for the therapeutic approach, revealing the type of articular involvement.

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COMPLEMENT SYSTEM IN PSORIATIC ARTHRITIS: A USEFUL MARKER AND A POTENTIAL THERAPEUTIC TARGET OF ANTI-TNF-ALPHA TREATMENT

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Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis. Pathogenesis is incompletely understood and TNF-α produced by macrophage infiltration may be the origin of hypersensitize the synovium to endogenous ligands of the immune system. During joint inflammation, products resulting from complement activation may contribute to the development of cartilage injury. However, the role of complement in PsA is not completely understood. The aim of this study was to evaluate complement during anti-TNF-α treatment in PsA patients. 55 PsA patients treated with anti-TNF-α were enrolled. In all participants, serum complement components C3 and C4, C3 cleavage fragments, ESR and CRP were evaluated at baseline and after 22 weeks of treatment with anti-TNF-α. After 22 weeks a significant reduction in C3 and C4 serum levels was observed (p<0.005). C3 complement cleavage fragments were never detected. No differences were seen among data concerning the two biological treatments. Interestingly, serum complement C3 and C4 levels correlated with systemic parameters of arthritis activity (ESR and CRP levels, DAS28, SpAHAQ and PASI). Serum concentrations of complement system were reduced by anti-TNF-α treatment and were as sensitive as ESR, CRP levels, or clinical joint scores in assessing treatment response. This is the first study demonstrating the therapeutic effect of anti-TNF-α in reducing complement components in serum of psoriatic arthritis patients (in the absence of complement cleavage fragments). This down-regulation of C3 and C4 by the treatment makes it possible to consider complement components a useful marker and a potential therapeutic target in PsA.

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EPSA QUESTIONNAIRE SENTITIVITY IN THE IDENTIFICATION OF EARLY PSORIATIC ARTHRITIS

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Background: CASPAR criteria are increasingly used to identify early psoriatic arthritis (ePsA). The aim of the study is to validate the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire in a early PsA cohort and compare with a new self-administred Early Psoriatic Arthritis questionnaire (EPSAq) in a dermatology clinics.
Methods: Cases of early PsA (less than 24 months symptom duration) and controls with psoriasis who were all disease modifying anti-rheumatic drug naïve were recruited. Gold standard diagnosis was confirmed by a rheumatologist.
A 66/68 joint count, enthesitis count (MASES) and assessement of axial disease (BASMI) were performed to assess presence of inflammatory disease. Patients were screened with PASE and EPSA questionnaire. A multidisciplinary team of dermatologists and rheumatologists were involved in the design of EPSA questionnaire based on 14 items.
Results: 100 early PsA cases and 70 psoriasis controls were recruited from a the Psoriasis Clinic in the Dermatological Departement. In patients with PsA the median total PASE score was 44 (25^{th} and 75^{th} percentiles, 38 and 51 respectively), whereas median EPSAq score was 7 (5-10). Using receiver operator curves, we determined that EPSAq is more specific and sensitive than PASE questionnaire in our cohort to determine early PsA (p=0.001). A cut-off value of 5 in EPSAq achieved a sensibility of 83% and a specificity of 82% to discriminate ePsA.
Conclusions: The EPSAq is a fast self-administred questionnaire to screen early PsA patients among patients with psoriasis. A larger study in dermatology clinics is needed to validate EPSAq.

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SERUM MMP-3 LEVELS CORRELATE WITH DISEASE ACTIVITY IN ENTHESITIS RELATED ARTHRITIS (JIA- ERA): CROSS-SECTIONAL AND LONGITUDINAL STUDY

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Objective: To study serum MMP-3 levels and MMP-3/TIMP-1 ratio as markers for disease activity in JIA ERA.
Methods: 54 patients with JIA ERA (ILAR criteria) were studied. Baseline disease activity measures included tender and swollen joint counts, Maastricht Ankylosing Spondylitis Enthesitis Score, BASDAI, BASFI, Patient assessment of pain and global disease activity and Physician global assessment of disease activity and ESR. Serum MMP3 and TIMP1 levels were measured using ELISA. 24 patients were followed up for longitudinal study. Statistical analysis was done using non parametric tests.
Results: Of 54 patients, 48 were males; The mean age at onset of disease was 11.8±4.19 years and duration of disease was 5.2±4.3 years. Majority of patients had active disease at baseline with a mean ESR of 72.4±33.6 mm/hr and mean BASDAI of 3.7±1.95. The median MMP-3, TIMP-1 and MMP-3/TIMP-1 ratio were 50.4 ng/ml (13.0-193.8 ng/ml), 228.9 ng/ml(108.2-290.4 ng/ml) and 0.3 (0.07-1.13) respectively.
At baseline assessment MMP-3 levels directly correlated with various disease activity measures; TJC(r=0.60), SJC(r=0.45), BASFI(r=0.29), BASDAI(r=0.32), ESR(r=0.49), Physician Global assessment(r=0.40), Patient pain VAS(r=0.28), Patient global assessment(r=0.38) (all p values <0.05). However MMP-3/TIMP-1 ratio correlated only with TJC, SJC and ESR(r=0.51, 0.39 & 0.34 respectively; $p<0.05$).
In the longitudinal study, change in MMP-3 correlated with change in TJC, SJC and ESR (r=0.42, 0.44, 0.54 respectively; $p<0.05$), but change in MMP-3/TIMP-1 ratio did not correlate with change in disease related measure.
Conclusion: MMP-3 is a reliable marker for disease activity in JIA ERA and can be used in follow up.

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CIRCULATING LEVELS OF THE ADIPOKINES VASPIN AND OMENTIN IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS, AND RELATION TO DISEASE ACTIVITY

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Objective: Vaspin and omentin are two recently discovered adipokines, that have been involved in chronic inflammatory processes. The aims of our study were to evaluate their serum levels in patients affected by juvenile idiopathic arthritis (JIA), in comparison to healthy controls, and to correlate circulating levels to parameters of disease activity.
Methods: Serum levels of omentin and vaspin were assayed by enzyme-linked immunosorbent assay in 40 patients with JIA classified according to the ILAR criteria and 26 healthy controls.
Results: Serum omentin levels were significantly higher in JIA patients versus healthy controls ($p<0.0001$, Figure 1) whereas serum vaspin levels did not significantly differ between the two groups. Serum omentin levels were significantly correlated with the presence of active joints ($p<0.0001$) and, in addition, JIA children with active joints showed higher serum levels than JIA children without active joints ($p<0.001$). Omentin serum levels were also significantly related with the number of active joints ($p<0.002$).
Conclusions: Our study is the first report on the new adipokines vaspin and omentin in patients with JIA, and it shows that omentin is significantly higher in JIA patients in comparison with healthy controls. In addition, we also report that omentin plasma levels are significantly correlated with the presence and also with the number of active joints.

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CAUSES OF MISDIAGNOSIS IN FIBROMYALGIA

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Fibromyalgia is a syndrome characterized by widespread pain and tenderness in at least 11/18 tender points. These two defining features are accompanied by an array of multisystem symptoms which can make more complicated the differential diagnosis.
Aims of this study have been to investigate the more common reasons of misdiagnosis with other rheumatic diseases in order to improve the accuracy of diagnosis.
One-hundred-twenty-four outpatients fulfilling ACR criteria for Fibromyalgia were evaluated. Twenty-five patients were previously misdiagnosed as inflammatory arthritis (n=11), Connective Tissue Disease (CTD) (n=8) and spondyloarthropathies (SpA) (n=6); in these patients, cause of misdiagnosis were respectively wrong interpretation of ultrasonographic changes, autoantibodies pattern and MRI alteration of sacroiliac joint.
A significant difference in ESR values ($p=0.042$), latency of diagnosis ($p=0.018$), disease duration ($p=0.02$) and age $p=0.05$) was observed between case and control group;. CRP was altered in 8% and ANA in 20% of misdiagnosed patients. As expected, no differences were found in the clinical features and clinimetric scores between 25 misdiagnosed patients and the other 99 Fibromyalgia patients with the exception for number of tender points that were higher in misdiagnosed group ($p=0.009$) due to the incorrect treatment. Even if Fibromyalgia is a well known, separate clinical entity, differential diagnosis with SpA, CTD and inflammatory arthritis could still represent a challenge for rheumatologist. In order to prevent misdiagnosis and mistreatment of patients, clinician should be alerted to consider diagnosis of Fibromyalgia in patients presenting with ill-defined symptoms and signs.

Posters

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HLA-B*27 ALLELE ASSOCIATED ANTERIOR UVEITIS TO BEHÇET'S DISEASE IN MOROCCAN PATIENTS

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Behçet's disease (BD) is an inflammatory disorder of unknown cause, characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions. A close association of the Human Leukocyte Antigen HLA-B51 allele with the disease suggests that genetic predisposition contributes to susceptibility to BD in different ethnic populations. To analyze the influence of HLA-B alleles in BD predisposition in Moroccan population and its association with clinical manifestations.
The HLA-B phenotype frequencies were analyzed by serologic HLA class I typing and by polymerase chain reaction sequence-specific oligonucleotide (PCR-SSO) reverse dot blot hybridization in 120 unrelated Moroccan patients There were 84 males (70%) and 36 females (30%). Age ranged from 14 to 53 years (mean: 31 years, sex ratio: 2.33); all of whom fulfilled the international study group criteria for Behçet's disease, and in 112 ethnically matched healthy controls.
Besides HLA-B*51 allele (20%), a significant increased frequency of the HLA-B*27 allele was found in Moroccans patients with Behçet's disease when compared to controls (13.33% of patients versus 2.67% of controls, chi square = 8.75, OR=5.59, 95% IC [1.58-19.75] and particularly in the patients who presented an anterior uveitis (25 % vs. 5.55%, p<0.005).
Our results suggest that HLA-B*51 and HLA-B*27 allles could be associated with Behçet's disease in the Moroccan population, however the implication of the other genes in the predisposition in the disease remains possible.

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INCREASE OF MICRO-RNAS-223 IN TWO RHEUMATOID ARTHRITIS PATIENTS AFTER 6-MONTH-ADALIMUMAB THERAPY

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Introduction: MicroRNAs (miRNAs) are regulators of gene expression at post-transcriptional level. Abnormal expression of miRNAs was reported in rheumatic diseases. We recently demonstrated that miR-223 is up-regulated in CD3+lymphocytes from Rheumatoid Arthritis (RA) patients compared to healthy controls.
Objective: To evaluate possible serum changes of miRNA-223 in two RA patients after 6 months of adalimumab-therapy.
Methods: We studied 2 female RA patients (62 and 66 years respectively), with one-year-disease duration and active disease (DAS28 6.78 and 6.99 respectively). At baseline, one patient was taking no drug, the other 4 mg/day of metilprednisolone and 10 mg/week of MTX. MiR-223 expression in CD3+ T-lymphocytes was analyzed. MiR-223 values are reported as fold change. Total serum RNA was extracted with QIAamp Circulating Nucleic Acid Kit (Qiagen) using a supplementary protocol for isolation of circulating miRNA. qPCR is performed following miScript PCR System (Qiagen) and expression level of miR-223 is calculated with Vandesompele Method. Adalimumab was prescribed at standard dosage.
Results: After 6 months, clinical evaluation, blood analyses and serum levels of miR223 were again performed. The expression of miR-223 was increased in both patients. At baseline, miR-223 levels were 1.00±0.043 in the first patient and 1.00±0.232 in the other, after 6 months, miR- 223 levels were 2.91±0.216 and 41.98±3.846 respectively.
Conclusions: MiR-223 expression is myeloid-specific. TNF is an important cytokine produced by macrophages during inflammation. We hypothesize that miR-223 increase is probably due to the apoptosis of myeloid cells after anti-TNF-therapy.Further studies are required to confirm our preliminary results.

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EVALUATION OF MS GENETIC COMPLEXITY BASED ON THE ANALYSIS OF THREE IMMUNE-ASSOCIATED POLYMORPHIC SYSTEMS

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Multiple sclerosis (MS) clusters with the so-called complex genetic diseases with autoimmune component. The aim was to evaluate the role of genetic polymorphisms of three immune-related systems - cytokines, NK receptors and their HLA ligands in MS pathogenesis. 58 patients and 104 healthy individuals from the Bulgarian population were genotyped for HLA- B, C, DRB1, DQB1, KIRs, TNF-α, TGF-β, IL-10, IL-6, IFN-γ.
In addition to previously found predisposing effect of DRB1*1501-DQB1*0601 haplotype to MS, DQB1*02 allele and DRB1*13-DQB1*03 haplotype also showed a positive disease association. Significantly increased frequencies of HLA-B*15 (p=0.036), B*73 (p=0.007) and Cw*15 (p=0.016) were found in MS. Individuals homozygous for group 2 HLA-C ligands were more frequent among patients (p=0.05). A tendency for prevalence of KIR2DS1 in MS in comparison to healthy subjects (46.3% vs. 33.3%) and an increased frequency of KIR2DS1/C2 ligand combination (p=0.039, OR=3.52) were observed. A significant increased CC genotype of IL-10 -819 and -592 SNPs coupled with a decreased frequency of the TGF-β +915 CG genotype in MS patients (Pc<0.05) was found.
Data implies that additional HLA alleles could be predisposing for MS. Distinct KIR or KIR/HLA-ligand combinations may be relevant to the development of autoimmunity in the manner that the activation overrides inhibition of NK and NKT cells. Polymorphic variations of IL-10 and TGF-β may play a role in MS susceptibility through dysregulation in Th2 profile. The cumulative effect of studied genetic markers seems to be important for disease pathogenesis but which of them may play primary role remains controversial.

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AGE-SPECIFIC FAMILIAL RISKS OF RHEUMATOID ARTHRITIS: A NATION-WIDE EPIDEMIOLOGICAL STUDY FROM SWEDEN

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Objective: Familial risks of rheumatoid arthritis (RA) have been assessed in small case-control studies, usually based on reported, but not medically verified, RA in family members; thus the degree of familial clustering of these diseases remains to be established.
Methods: The Multigeneration Register, in which all men and women born in Sweden from 1932 onward are registered together with their parents, was linked to hospital admission data. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed to the expected number of cases of men and women with mothers and/or fathers affected by RA, compared with men and women whose mothers and/or fathers were not affected by RA.
Results: A total of respectively 18,496 and 51,921 cases of RA were recorded in offspring and parents. The overall significant SIRs among men and women with a mother, father or both parents hospitalized for RA varied between 2.64 and 11.01. Marginally higher familial risk was found before age 40. The risk was not dependent on gender. The parental transmission of RA was similar for both men and women. The population attributable fraction of familial RA was 4.29%.
Conclusions: This study has provided the first data on age-specific familial clustering of RA, based on medically confirmed records. The risks were so high that hereditary factors were considered to be likely to contribute, possibly modified by environmental factors. Age-specific risk tables would be helpful for clinical counseling.

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MYOFIBROBLAST SPECIFIC GENE EXPRESSION SIGNATURE IN SYSTEMIC SCLEROSIS, MORE THAN TGF-BETA INDUCED ACTIVATION

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Background: The key cells in the pathogenesis of tissue fibrosis are myofibroblasts. Their number is increased in systemic sclerosis (SSc) skin and correlates with

the severity of skin fibrosis. Our purpose was to unravel the specific transcriptome of myofibroblasts derived from SSc skin biopsies.
Methods: Fibroblasts were subcultured from a forearm biopsy of 4 early diffuse SSc patients and used at passage 3. 250 alpha-SMA positive cells were isolated by laser capture microdissection (LCM) for Microarray analysis and qRT-PCR validation. Immunofluorescence (IF), followed by confocal laser scanning microscopy (CLSM), was conducted for validation of the mRNA results. TGF-beta stimulation experiments were conducted on normal dermal fibroblasts.
Results: qRT-PCR showed a mean 3.7 fold increased expression of alpha-SMA in the LCM captured cells. Microarray analysis identified 269 genes upregulated more than 2 fold in the myofibroblasts. Besides predictable genes involved in the increased ECM production and TGF-beta pathway activation, genes not classifiable in any specific functional pathway were identified. They comprised tropomyosin, reticulocalbin-1, caldesmon-1 and Neuroblastome Breakpoint Family (NBPF). CLSM confirmed the expression, never shown before, of NBPF in dermal fibroblasts and demonstrated a specific expression profile of caveolin-1 and phospho-RB. Functional studies indicated that NBPF was not inducible by TGF-beta stimulation neither at mRNA or protein level.
Conclusions: Myofibroblast transcriptome displayed genes involved in several pathways not known to be specific of myofibroblasts or inducible by TGF-beta. The specific expression of these genes may reflect either a specific metabolic status or a specific differentiation lineage of myofibroblasts.

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PRESENCE OF SHARED EPITOPE IN A COHORT OF EGYPTIAN RHEUMATOID ARTHRITIS PATIENTS AND ITS RELATIONSHIP TO CLINICAL AND SEROLOGICAL FINDINGS

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An association between RA and the Class II HLA proteins was first noted in the 1970s, when the mixed lymphocyte culture (MCL) type Dw4 was observed to be more common among patients with RA compared to controls. In 2004, Begovich *et al*. identified an arginine to tryptophan amino acid change in PTPN22 that was strongly associated with risk of RA. The MHC "shared epitope" alleles and the PTPN22 variant contribute to risk in a subset of RA patients with autoantibody-positive disease. Aim this work is to detect the presence of the shared epitope in 30 RA patients and correlate this with disease state.
RA patients were examined for their clinical state, disease activity, radiologic evaluation and laboratory parameters. We used the (PCR) to detect the HLA-DRB1 alleles, then we checked the amino acid sequence at positions 70-74 to detect the presence of the shared epitope. Patients were compared to a group of 200 normal Egyptian healthy volunteers presented to the nephrology unit for kidney donors. We observed that HLA-DRB1*15 was a common tissue typing in our RA patients and is noted to be well correlated to clinical course of the disease as well as serological markers and radiological progression.
Conclusion: DR15 is the most frequent HLA typing observed in the studied cohort of Egyptian rheumatoid arthritis patients. QARAA is the most frequently detected shared epitope. This was found to be well correlated to the inflammatory markers of the disease severity and the parameters of the radiologic progression.

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HLA CLASS II, MICA AND PRL GENE POLYMORPHISMS: THE COMMON CONTRIBUTION TO THE SYSTEMIC LUPUS ERYTHEMATOSUS DEVELOPMENT IN CZECH POPULATION

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The genetic components contribute to the Systemic lupus erythematosus development. This study for the first time determined the distribution of the polymorphisms and linkage disequilibrium in HLA class II, MICA and PRL gene among patients suffering from SLE and healthy Czech individuals.
DNA was obtained from the peripheral blood cells of 123 SLE patients and 96 healthy people. Allele variants of the HLA class II, MICA transmembrane polymorphism and PRL extrapituitary promoter -1149G/T SNP were detected using the sequence specific primers analysis, PCR-fragment analysis and PCR- RFLP, respectively.
In Czech population only DRB1*03-DQB1*0201 haplotype is significantly associated with increased risk for SLE development: the frequency in SLE group was 44.7% in comparison to 15.2% in controls, p_c<0.0001; OR 4.54 CI 95% (2.36-9.09). The MICA-A5.1 allele is present significantly more often in SLE (55.7%) than controls (39.9%), p_c=0.005; OR 1.88 CI 95% (1.29-2.77) and the combination of HLA DRB1 *03 together with MICA-A5.1 is strongly associated with SLE [p_c <0.000001; OR 9.71 CI 95% (3.4-27.7)]. The combination of absence MICA-A6 together with HLA DRB1*11 seems to be risk for SLE development compared to controls, 84.6% and 70.2% respectively, [p_c=0.0003 OR 2.32 CI 95% (1.47-3.70)]. We found that only G allele of the -1149 G/T SNP is associated with specific clinical manifestation of SLE, arthritis [p_c=0.022; OR 2.63, CI 95% (1.45-4.81)]. HLA class II-MICA combinations may increase/decrease a risk for SLE development.
This study was supported by the Czech Ministry of Health—Research Project MZO 00023728.

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IS METHYLATED DSDNA VACCINATION A FEASIBLE TREATMENT FOR AUTOINFLAMMATORY, AUTOIMMUNE DISEASES, AND SOME CANCERS?

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Lymphocyte & Cellular apoptosis, is immunosuppressive, necrosis is immunoenhancing. The former is associated with methylated dsDNA, the latter with inflammation and demethylated DNA. Corticosteroids, renal dialysis, immunosuppressive agents, antigens, TNF-α, anti TNFs, B cell monoclonal antibodies, anti T cell antibodies, anti Thymoglobulin (ATG), and pregnancy are all associated with apoptosis, immune-suppression, and free DNA in the plasma. In pregnancy this is of fetal origin, increases with each trimester, & is associated with remission of RA and Lupus, with relapse after delivery. Regulator suppressor T cells (TRegs) are reduced in frequency or function in RA and SLE, Crohns disease, and also in pregnancy, and return to normal following delivery. "Therakos" photopheresis utilizes methoxypsoralen and UVA to cause cellular apoptosis, followed by iv. infusion of these apoptotic cell fragments in successfully treating cutaneous T cell lymphoma (CTCL), a monoclonal T cell disease driven by demethylated DNA. Vasogen has used a similar technique " Celacade" for treating heart failure. The success of photopheresis therapy in CTCL has prompted its use with some success in cutaneous Lupus, Rheumatoid Arthritis, Scleroderma, Transplant Rejection, and hyperactive airways disease. The mechanism of its action has not been completely defined. If the mechanism of this immunosuppression is due to methylation of this native mammalian dsDNA, then one would expect this dsDNA to be non antigenic, immunosuppressive, and an activator of suppressor regulator T cells. It is (abstract #) Mammalian & apoptotic dsDNA is methylated.

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MICROARRAY SCREENING FOR 727 MICRORNAS IN PERIPHERAL BLOOD T LYMPHOCYTES OF LIMITED SYSTEMIC SCLEROSIS PATIENTS

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Introduction: Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease characterized by excessive collagen deposition in the skin and internal organs. MicroRNAs (miRNAs) are functional small RNA which regulate gene expression at post-transcriptional level.
Objective: To find a correlation between miRNA expression pattern of blood peripheral T-lymphocytes with SSc pathogenesis.
Methods: We studied 5 patients (3 females, 2 males, median age 64.4±5.8) affected by limited SSc compared to 3 healthy controls (2 females, 1 male, median age 35.3±8.0). Circulating T lymphocytes were isolated with Lympholythe-H (Cederline) and Pan T Cell Isolatin Kit (Milteny). Total RNA was extracted with TRIzol (Invitrogen) and microarray analysis was performed by Microarray Facility - Ferrara.
Results: Among 727 different miRNAs evaluated in T-lymphocytes, some miRNAs resulted under-expressed in SSc patients respect to healthy controls (374b, 30e*, 194, 128, 106a, 20a*, 424, 95, 505, 10a, 31*, 362-5p, 650) and some miRNAs over-expressed (766, 574-5p, 574-3p, 34a). In silico analysis through on-line database showed that all these miRNAs are involved in regulation of growth factors and cell signaling.
Conclusions: Further studies are in progress to confirm microarray analysis and to elucidate the role of miRNAs in SSc, but our results open the way for future utilization of miRNAs as useful disease markers or as therapeutic targets.

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EFFECT OF COMBINED GENOTYPES FOR FC GAMMA RECEPTOR POLYMORPHISMS IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS FROM WESTERN INDIA

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Aim: To identify genotype frequencies of activating Fc g receptors (IIA and IIIB) and inhibitory receptor (IIB) polymorphisms in Systemic Lupus Erythematosus (SLE) patients from Western Mumbai, India and to correlate them with clinical severity of disease.
Material and methods : Eighty five SLE patients fulfilling ACR criteria from Mumbai, India were included along with eighty five age and sex matched normal healthy individuals. Genomic DNA was extracted and Fc g receptor IIA, IIB and IIIB polymorphisms were identified using allele specific primers by PCR and RFLP techniques. Autoantibodies such as ANA, anti-dsDNA, anti-histone and ANCA were detected by IIF, ELISA and ANA-BLOT, Euroimmune, kits.
Results: Fc g receptor IIA polymorphism showed R/R 131 in 10%, R/H 131 in 62.5% and H/H 131 is 27.5% in Western Indian population as compared to 20%, 70% and 10% in SLE patients respectively. Fc g R IIB genotype frequency was 61.2% for Ile/Thr, 20.0% for Thr/Thr and 18.8% for Ile/Ile in SLE as compared to 65%, 12.5% and 22.5% respectively among normals. Fc g receptor IIIB polymorphism among SLE patients showed allele frequency for NA2/NA2 to be 40 % where as NA1/NA1 genotype frequency was the lowest (10%). The correlation of Fc g receptor IIA, IIB and IIIB genotypes with clinical manifestations and autoantibody profile and the effect of combined frequencies will be presented.
Conclusion: This is the first study on SLE patients from Western India to identify distribution Fc g receptor polymorphisms to understand immunogenetics underlying etiopathogenesis of SLE.

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INFLUENCE OF -308 PROMOTER POLYMORPHISM OF THE TNF-A GENE ON THE EXPRESSION OF HMGB-1 IN RHEUMATOID ARTHRITIS AND SPONDYLOARTHRITIS PATIENTS

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Single nucleotide polymorphism in the human Tumor Necrosis Factor-α (TNF-α) gene promoter, the -308 G/A variant, has been associated with increased susceptibility to and severity of rheumatoid arthritis and to poor responsiveness to TNF-α blockade therapy. High Mobility Group Box Protein (HMGB-1) is a pro-inflammatory cytokine that plays a pivotal role in the pathogenesis of rheumatoid arthritis and may be an original target of therapy. The aim of the study was to investigate whether the -308 G/A variant of the TNF-α gene is associated with altered expression of HMGB-1. A total of 110 consecutive patients with rheumatoid arthritis and spondyloarthritis were enrolled. They were genotyped by Polimerase Chain Reaction (PCR) for the -308 TNF-α gene promoter polymorphism. Clinical status was also assessed. HMGB-1 and TNF-α mRNA (Real Time PCR) from leucocytes and HMGB-1 protein (Western Blot analysis) and TNF-α mature protein (ELISA) in blood were evaluated. Irrespecting of the underlying disease, patients carrying the G/A genotype showed enhanced HMGB-1 and TNF-α mRNA levels and increased circulating concentration of the inflammatory cytokines when compared to patients with G/G genotype. The data suggest that humans with a TNF-α-308 G/A genotype have enhanced expression of HMGB-1 protein that may explain, at least in part, the enhanced severity of the disease.

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PATHOGENESIS OF IDIOPATHIC RECURRENT PERICARDITIS AND ROLE OF THE TNFRSF1A GENE MUTATIONS

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Background: Although many causes of pericarditis are recognized, the etiology remains obscure in about 85% patients and it is therefore labelled as idiopathic. Recurrent pericarditis is common in familial Mediterranean fever (FMF), due to mutations in the MEFV gene, and tumor necrosis factor receptor-associated periodic syndrome (TRAPS), due to mutations in the TNFRSF1A gene, but it rarely occurs alone. Colchicine is the standard treatment for FMF, while patients with TRAPS do not respond to colchicine therapy. Colchicine has been also proposed for the treatment of recurrent pericarditis and decreases the recurrence rate. Our aim was to investigate a possible involvement of TNFRSF1A mutations in patients with recurrent pericarditis
Methods: 102 patients were enrolled; 30 of 102 were characterized by a poor response to colchicine. Mutations of *TNFRSF1A* were searched for
Results: TNFRSF1A mutations were found in 7 of 92 patients. Four out of 7 were refractory to colchicine and 2 of 7 patients had a family history of pericarditis (they were siblings). One of the 7 patients carried a novel deletion (ΔY103-R104), 5 patients carried a low-penetrance R92Q mutation and 1 patient carried a V95M mutation.
Conclusions: Our data suggest that TRAPS should be kept in mind in the differential diagnosis of recurrent pericarditis. A poor response to colchicine treatment, and a positive family history may indicate the need to investigate mutations in the TNFRSF1A gene. However, to date, further studies are needed in order to better determine additional criteria for identifying the few subjects who might carry such mutations.

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ROLE OF AIRE IN THE ORGANIZATION OF THYMIC MICROENVIRONMENT

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The roles of Aire-expressing medullary thymic epithelial cells (mTECs) in the organization of the thymic microenvironment for establishing self-tolerance are enigmatic. We sought to monitor the production and maintenance of Aire-expressing mTECs by a fate-mapping strategy in which bacterial artificial chromosome transgenic mice expressing Cre recombinase under the control of the Aire regulatory element were crossed with a reporter strain for GFP expression. We found that, in addition to its well-recognized expression within mature mTECs, Aire was expressed in the early embryo before emergence of the three germ cell layers. This observation may help to explain the development of ectodermal dystrophy often seen in patients with AIRE deficiency. With the use of one transgenic line in which Cre recombinase expression was confined to mTECs, we found that Aire-positive/CD80-high mTECs further progressed to an Aire-negative/CD80-intermediate stage(s), suggesting that Aire expression is not constitutive from after its induction until cell death but is temporally circumscribed at the beginning of terminal differentiation.

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NATURAL KILLER AND B CELLS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND PSORIATIC ARTHRITIS TREATED WITH ETANERCEPT

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Modifications of innate and adaptive immune cells in Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PSA) during biologic treatment are fundamental to understand disease pathogenesis. The aim of this study was to assess the cell subpopulation and autoantibodies at different time points in a cohort of RA and PSA patients treated with Etanercept. The number and frequency of CD16+ CD56+ NK cells, CD19+ B cells was studied by flow cytometry in the peripheral blood of 84 RA, 32 PSA and 45 healthy subjects. Sera were tested for Rheumatoid Factor, anti-CCP antibodies, ANA, anti-ENA and anti-cardiolipine IgG/M antibodies. A reduction of NK and B cell number was demonstrated in RA (p=0.01, p=0.0003) and PSA (p=0.008, p=0.003) patients compared with healthy subjects. An increase of the absolute number and frequency of NK cells was demonstrated in RA patients treated with Etanercept at week 14 (p=0.01), 22 (p<0.01), 54 (p<0.01) and 102 (p<0.01). PSA patients treated with Etanercept showed an increase of the number and frequency of NK cells at week 54 (p<0.05) and 102 (p<0.01). Moreover, an increase of CD19+ B cells was demonstrated in RA (p=0.01) and PSA (p<0.05) patients treated with Etanercept at week 14 associated with ANA production. These data demonstrated for the first time that Etanercept increased NK and B cells in the peripheral blood of RA and PSA patients. This could be explained by the attempt to restore both the innate and adaptive immune compartments.

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FAMILIAL MEDITERRANEAN FEVER AND AUTOIMMUNE / RHEUMATIC DISEASES

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Familial Mediterranean fever (FMF) is an autosomal recessively inherited autoinflammatory disorder caused by MEFV gene missense variations, which results in an alterate control of innate immune response. Arthritic involvement may be the onset symptom and simulate any rheumatic disease; moreover MeFV mutation may worse clinical features of concomitant autoimmune diseases, as Inflammatory Bowel Diseases, chronic polyarthritis, Behçet disease, juvenile idiopathic arthritis (JIA) or negative HLA-B27 antigen ankylosing spondylitis (AS), although the pathogenic mechanism of this association still remains unknown.
In our seies of 288 FMF patients ,we describe our experience of patients with rheumatic/articular diseases and FMF diagnosis, established before onset of rheumatic sympthoms or delayed by them, in most cases; moreover FMF-related MEFV mutations are associated with HLA negative AS and demostrate that the presence of MeFV mutation may cause an excessive immune response in which the spontaneous ignition tends to stray towards the autoimmunity.
The introduction of the concept that the innate response modulate the cytokine network, allowing to clarify the ethiopatogenesis of these conditions. In fact, it has shown that an altered balance of pro-inflammatory cytokines may promote autoimmune diaseases Indeed the administration of biological drugs, allowed to achieve good control of both kind of diseases.

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MICROCHIMERISM IN AUTOIMMUNITY: DETECTION METHOD BASED ON QPCR ANALYSIS OF INSERTION-DELETION POLYMORPHISMS

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Introduction: Microchimerism is an intriguing phenomenon playing a role in autoimmune diseases such as systemic lupus erythematosus. We here present a technique based on the detection of a mismatch in polymorphisms applying a previously described set of bi-allelic insertion deletion polymorphisms (Indels) by quantitative polymerase chain reaction (qPCR) (Alizadeh, Blood 2002).
Methods: Twenty couples consisting of related subjects (parent and child) donated oral mucosal cells for the determination of the presence of Indel polymorphisms from our selected set. These Indels are bi-allelic polymorphisms that are common in the population and are located on 9 different chromosomes.
Results: Using the Indel-set we were able to distinguish child from parent in 82% of cases. Some of these primers were not informative in our population and can thus be excluded. For the informative primers a sensitivity of 1:100.000 genome equivalents and a specificity of 100% could be reached using qPCR with SYBR Green intercalation.
Conclusion: Detection of microchimerism is technically challenging. It requires the presence of allogeneic markers and a method with high specificity and sensitivity. Using real-time qPCR with SYBR Green intercalation to detect microchimerism based on different Indels, we were able to distinguish offspring derived chimeric cells in healthy individuals with a sensitivity of 1:100.000 genome equivalents. This technique bypasses gender-mismatch limitations, and is applicable for research on chimerism in renal transplantation and autoimmunity.

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HIGH LEVELS OF MATERNAL SERUM IL-17, IL-6, IL-10, TNF-ALPHA IN PREGNANT WOMEN AFFECTED BY SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: To evaluate serum changes of IL-17 , IL-6, IL-10, TNF-α in women with systemic lupus erythematosus (SLE) during pregnancy.
Methods: A group of SLE patients (n=15) and healthy controls (n=15) were longitudinally studied. We collected blood samples before and during pregnancy (8-12; 20-24; 37-40 weeks). Serum IL-17, IL-6, IL-10, TNF-α concentrations were evaluated by specific ELISA.
Results: Serum IL-17, IL-6, IL-10 and TNF-α resulted significantly higher in women with SLE before pregnancy (p<0.001). During gestation, serum IL-17 levels were found higher in SLE patients than in controls, with no changes during pregnancy. IL-6 increased in both groups, resulting higher in SLE patients than in controls only in the first trimester (p<0.05). IL-10 concentration in SLE progressively increased during pregnancy resulting constantly significantly higher than in controls (p<0.01). TNF-α levels were higher in SLE group than in controls in third trimester (p<0.01).
Conclusion: SLE women showed an increased of IL-17, IL-6, IL-10 and TNF-α during gestation, with a different trend for the various cytokines. These data suggest that patients with SLE have a hyper-reactive immune system during pregnancy, probably due to placenta secretion too.

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COMP, STNF-RII AND IL-6 LEVELS IN RELATION TO SERUM ESTRADIOL, FUNCTIONAL AND RADIOLOGIC FINDINGS IN POSTMENOPAUSAL FEMALES WITH KNEE OSTEOARTHRITIS

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Aim of the work: To evaluate relation between serum levels of cartilage oligomeric matrix protein COMP, sTNF-RI1, IL-6 and estradiol in post-menopausal females with osteoarthritis
Subjects and methods: Twenty post-menopausal females (PMOA) with clinically and radiologically knee osteoarthritis were compared to post-menopausal females (control group (1)) and ten pre-menopausal females (control group (2)) who were clinically and radiologically free of knee osteoarthritis. To all the studied subjects, a complete clinical examination was performed, COMP, sTNF-RII, IL-6, and estradiol levels were estimated
Results: The mean serum COMP was slightly higher in the PMOA group than in control group (1), and both means were significantly higher than mean value in control group (2). The mean sTNF-RII value was significantly higher in the PMOA group than in control group (1) and control group (2). Mean serum IL-6 value was significantly higher in control group (1) than in the both PMOA and control group (2). ROC curve in PMOA and control group (1) revealed that both serum COMP and sTNF-RII had diagnostic specificity of 90% each, while the diagnostic sensitivity was 45% and 50% respectively. By using the combined approach, the diagnostic sensitivity of COMP and sTNF-RII raised to 90% and 83% respectively. ROC curve analysis of the same parameters in PMOA and control group (2), revealed a diagnostic sensitivity of 100% for each of serum COMP and sTNF-RII as well as diagnostic specificity of 90% and 70% respectively.
Conclusion: Combined measurement of COMP and sTNF-RII may be used in identifying osteoarthritis in post-menopausal females.

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MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) ENHANCES OSTEOCLASTOGENESIS THROUGH UPREGULATION OF RANKL EXPRESSION FROM SYNOVIAL FIBROBLASTS IN RHEUMATOID ARTHRITIS

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Objective: Macrophage migration inhibitory factor (MIF) has been shown to be a key regulator of acute and chronic immunoinflammatory conditions including rheumatoid arthritis (RA). We examined the effect of MIF on osteoclastogenesis, which is known to play a crucial role in bone destruction in RA.
Methods: The concentration of MIF and RANKL in the synovial fluid was measured by ELISA. Synovial fibroblasts were isolated from RA patients and the expression of RANKL was determined by real-time PCR and western blot. Osteoclastogenesis was analyzed in cocultures of rhMIF-stimulated RA patients synovial fibroblasts with human monocytes pretreated with monocyte-colony stimulating factor (M-CSF).
Results: MIF concentrations in RA synovial fluid were significantly higher than those in osteoarthritis (OA). The level of RANKL also correlated with that of MIF in RA synovial fluids (r=0.6, p<0.001). MIF could upregulate the expression of RANKL in RA synovial fibroblasts, which was partially blocked by interleukin (IL)-1b neutralization. Osteoclastogenesis was increased after coculture of MIF-stimulated RA synovial fibroblasts with M-CSF-treated monocytes and this was diminished by RANKL neutralization. Blocking of phosphoinositol-3 kinase (PI3K), p38 mitogen-activated protein kinase (p38 MAPK), Janus kinase-2 (JAK-2), NF-

kB, and activator protein-1 (AP-1) also led to a marked reduction in RANKL expression and osteoclastogenesis. Thus, MIF had the potential to induce joint destruction via PI3K, p38 MAPK, NF-kB, and AP-1.
Conculsions: The interactions among MIF, RA synovial fibroblasts, osteoclasts, RANKL, and IL-1b expression may be a potential gateway leading to new therapeutic approaches in treating bone destruction in autoimmune arthritis.

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IL-32 IS PRESENT IN THE INFLAMMATORY MILIEU OF ALLERGIC RHINITIS

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Interleukin (IL)-32 is a recently described proinflammatory cytokine produced by T lymphocytes, natural killer cells, monocytes, and epithelial cells. It has been reported that IL-32 plays an important role in various inflammatory diseases. However, the specific mechanism of IL-32 on allergic rhinitis (AR) has not been elucidated. To determine the role of IL-32 on inflammatory reaction of AR. IL-32 level was measured by ELISA method in serum, adenoid tissue, and nasal mucosa tissue from AR patients. The role of IL-32 was identified in AR animal model and eosinophils cell line, EoL-1 cells by using RT-PCR, ELISA, immunohistochemistry, luciferase assay, and caspase assay. In this study, we detected a significant increase of IL-32 protein and mRNA in the nasal mucosa of AR patients. The level of IL-32 staining is also highly expressed in AR nasal mucosa. In addition, in nasal mucosa tissue from AR patients, the level of IL-32 production correlated with inflammation, IL-1beta, IL-18, and granulocyte-macrophage colony-stimulating factor (GM-CSF). In AR animal model, IL-32 significantly increased IgE and inflammatory cytokine levels. IL-32 expression was induced by recombinant human GM-CSF via activation of caspase-1 in eosinophils. In addition, depletion of IL-32 prevents the production of inflammatory cytokines in eosinophils. In conclusion, IL-32 is a major inflammatory cytokine involved in the inflammation of AR. The regulation of IL-32 expression may form the basis of a new strategy for the treatment of AR.

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SECRETION OF PROINFLAMMATORY CYTOKINES

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Objectives: It was noted that treatment of a patient with acute mania by haloperidol was associated with marked improvement in activity of rheumatoid arthritis. The objective of this study was to examine the effects of haloperidol on inflammatory cytokine release *in vitro*, as a potential mechanism to explain the *in vivo* anti-inflammatory effects of haloperidol.
Methods: The effect of haloperidol on the production of inflammatory cytokines interleukin 1β (IL1β) and tumour necrosis factor α (TNF-α) was measured in bacterial lipopolysaccharide stimulated whole blood cultures and on the promonocyte cell line THP-1, using commercial and in house enzyme linked immunosorbent assays to measure cytokine concentrations.
Results: Haloperidol inhibited lipopolysaccharide stimulated production of both IL1β and TNF-α *in vitro* in a dose dependent manner and over a prolonged time period. Marked inhibition was seen over a range of concentrations of haloperidol from 0.5 μg/ml to 50 μg/ml, including those predicted to occur in the patient's blood.
Conclusions: Haloperidol treatment seemed to alleviate inflammation in rheumatoid arthritis. *In vitro* experiments would suggest that the mechanism is by direct inhibition of proinflammatory cytokine release. This phenomenon requires further investigation and may potentially lead to the development of novel treatment.

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PLASMA LEVELS OF IL-17 AND IL-23 IN IRANIAN PATIENTS WITH MULTIPLE SCLEROSIS

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Background and aims: Due to various studies on IL-17 and IL-23 in animal models of autoimmune diseases and humans, and also emerging data that support the crucial role for this lineage and related cytokines, this study aim is to investigate the difference between IL-17 and IL-23 plasma levels in MS patients.
Patients and methods: A total of 41 patients with MS were compared with 41 age and sex matched healthy control subjects. IL-17 and IL-23 in plasma samples were determined by Enzyme Linked Immuno Sorbent Assay (ELISA).
Results: The plasma levels of IL-17 (p=0.147) and IL-23 (p=0.245) had no differences between the 2 groups, while plasma levels of IL-23 in men were significantly (p=0.047) higher than in male healthy controls. Plasma levels of IL-17 and IL-23 were positively correlated in both patients and control subjects (p=0.0001 and p=0.048, respectively).
Discussion: No differences in plasma levels of IL-17 and IL-23 between MS patients and control group were shown overally which suggest that possibly small sample size, intrathecal synthesis of cytokines and delay in hospital admission following attacks all may contribute to obtaining these results. Meanwhile, a positive correlation between IL-17 and IL-23 in patients with Multiple Sclerosis and increased plasma level of IL-23 in male patients compared to male control group show that IL-23 plays a critical regulatory role in the differentiation and function of Th17 cells, that is, it enhances IL-17 production.

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LEPTIN, ADIPONECTIN AND RESISTIN: NEW CYTOKINES INVOLVED IN AUTOIMMUNE DISEASES?

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Aim: Cytokines play a crucial role in autoimmune diseases. Leptin, Adiponectin and Resistin are the best known adipokines, a new class of cytokine-like mediators produced by adipocytes. A significant role for such adipokines has recently been discovered in regulating immune responses and inflammation. Our aim was to detect the presence of Leptin Adiponectin and Resistin in the sera of patients affected by Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc) and Rheumatoid Arthritis (RA).
Methods: Sera samples were obtained by 20 SLE patients, 61 SSc patients, 19 RA patients and 23 healthy controls. Adiponectin was measured in all samples, Resistin was measured in RA- and SSC-samples, Leptin was measured in SSC-samples.
Results: Adiponectin levels showed a tendency to be increased in RA and SLE in comparison to healthy controls (p=0.15). On the other hand, Adiponectin was lower in SSc when compared to healthy controls (p<0.05). Resistin levels were lower in autoimmune diseases in comparison to healthy controls, with significant lower levels in the SSc group in comparison to healthy controls (p<0.05). Leptin levels were higher in SSc (p<0.05)
Conclusion: This study shows that Adiponectin and Resistin are present in lower concentration in SSc patients in comparison to healthy controls, while Leptin was found to be higher. No such a significant difference could be detected in this cohort for RA and SLE with regard to Adiponectin levels. Further analysis are needed in order to establish the real impact of adipokines on autoimmune diseases' course.

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EXPRESSION OF TELOMERASE VARIANTS AND DIFFERENT CYTOKINES IN B AND T CELLS OF PERIPHERAL BLOOD OF PATIENTS WITH SLE

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We tested quantitative expression of hTERT mRNA variants of T cells and B cells in lupus patients in comparison to healthy controls. We also evaluated quantitative expression of Bcl-2, CTLA-4, FoxP3, IL-4, IL-6, IL-10, IL-12, IL-17, IL-23, IFN-gamma and TGF-β.
T and B cells from 10 SLE patients and 7 normal counterparts were separated. Purity of separated cells was confirmed by flowcytometry. Total RNA and protein of separated cells was extracted to perform real time PCR and TRAP assay. Expression of desired genes was evaluated using specific primers and syber green I.
B cells in one patient and T cells in two other patients showed elevated expression of hTERT while none of healthy controls showed expression of telomerase in separated T and B cells. In B cells of SLE patient, the dominant variant was αβ-deletion whereas in T cells, no deletion and β-deletion variants were dominant. Telomerase protein activity confirmed results of mRNA expression. T cells of SLE patients showed decreased expression of FoxP-3, IL-4 and IL-10 in comparison to healthy counterparts (p<0.05) while B cells showed a significant increase in IL-10 expression (p<0.05).
Individualization of SLE patients regarding their expression pattern of hTERT vari-

ants may help to find individualized therapies for killing abnormal B and T cells. Significant reduction in Foxp3, IL-4 and IL-10 expression of T cells can contribute to induction of immune responses. Increasing IL-10 expression may be responsible for apoptosis induction in B cells and a mild decrease in Bcl2 support this finding.

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INCREASED SERUM IL-8 LEVELS IN BEHÇET DISEASE THAN NEUROBEHCET SYNDROME

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NeuroBehçet syndrome (NBS) is characterized by focal or multifocal parenchymal or peripheral nervous system involvement due to small vessels vasculitis or cerebral large vessel thromboses in patients with Behçet Disease (BD) and no alternative cause. Several immune mediators such as cytokines and chemokines have been identified to be involved in the pathogenesis of disease.
This study aimed to investigate the levels of serum Th1/Th2 cytokines in BD with or without neurological involvement.
Methods: Consisted of clinical evaluation of 13 patients with NBD and 17 patients with BD and the cross-sectional measurement of 11 Th1 and Th2 cytokines in their serum with a flow cytometry multiplex platform.
Our results showed that IL-8, IL-2 and IL-10 were the only detectable serum cytokines in any patient. IL-8 was detected in the 11 of 17 BD patients and 7 of 13 NBS patients, but the levels had a tendency to be higher in BD patients. The two NBS with highest IL-8 levels also had detectable IL-2. There was no correlation between activity of disease and IL-8 levels.
In conclusion, our results do not corroborate reports that showed a correlation between IL-8 and activity of BD. We were surprised to not detect serum TNF or IL-6.

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KANAMYCIN INDUCES SKIN IMMUNE REACTION

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Abuse of antibiotics to children associated with an increased risk of development of inflammatory diseases. The underlying mechanism to explain such association still remains to be clarified. Here, we show the mechanisms of kanamycin-induced skin inflammation in NC/Nga mice. NC/Nga mice were orally administered kanamycin for 7 days consecutively. Blood, spleen, and dorsal skin were taken on 18 weeks after the cease of kanamycin administration. Kanamycin significantly regulated allergic reaction-related factors such as histamine and IgE levels in the serum and IL-4 and IFN-γ productions in splenocytes stimulated with immobilized anti-CD3 antibody. We also observed the significant increases of the mRNA and protein expression of caspase-1 in the dorsal skin of the kanamycine-administered mice compared to the control mice. The activation of nuclear factor-κB and degradation of IkBa were increased by kanamycin administration. Kanamycin upregulated the TNF-α mRNA expression in the dorsal skin and the TNF-α production in stimulated splenocytes. Increased enzymatic activity of caspase-1 in the dorsal skin of the kanamycin-administered mice increased the mRNA expressions of IL-1β and IL-18. The productions of IL-1β and IL-18 were also increased in stimulated splenocytes in kanamycin-administered mice. Our findings suggest kanamycin use during infancy increases the potential source of skin inflammatory reaction through the up-regulatoin of caspase-1.

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THERAPEUTIC EFFECTS OF TGF-B-INDUCED REGULATORY T CELLS ON THE ESTABLISHED AUTOIMMUNE DISEASES

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Recent studies reveled injection of nTregs has less therapeutic effects on established autoimmune diseases. We now provide evidence that unlike nTregs, injection of iTregs markedly ameliorated the established autoimmune arthritis and lupus. Both antigen-specific and polyclonally induced iTregs suppressed the established CIA although antigen-specific iTregs had superior therapeutic effects. CIA mice given iTregs have significantly lower incidences of disease and clinic scores than control mice. While nTregs were converted into Th1/Th17 cells in vitro and in vivo in the inflammatory milieu, iTregs were resistant to T effector cell conversion. Injection of iTregs to naïve and immune deficient mice displayed similar levels of Foxp3 stability as comparing with nTregs. Of note, the stability of Foxp3 expression was only found in iTregs during established CIA. iTregs suppressed Th17 cell and osteoclast differentiation that paralleled with improved clinical scores, CII-specific IgG production and bone erosion. Injection of iTregs to established lupus mice significantly decreased the levels of anti-dsDNA and proteinuria, and markedly prolonged the survival of lupus. Blocking of TGF-β/TGF-βR pathway or anti-IL-10R antibody almost completely abolished the therapeutic effects of iTregs on lupus. We further observed that DC isolated from lupus mice received iTregs but not control cells expressed lower levels of CD80 and CD86 and adoptive transfer of these DCs suppresses lupus development. We therefore suggest that iTregs are stable and can target DC in the inflammatory milieu, these DC then have become tolerogenic DC and further suppress disease progression through its direct/indirect effect (inducing new iTregs) in autoimmune disease settings.

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TH17 IMMUNITY IN ALLERGIC ASTHMA

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Background: Allergic asthma is an inflammatory disease regulated by the T helper (Th) cells. The Th1/Th2 imbalance has been well documented in the pathogenesis of allergic asthma. Recently, Th17 cells have been found to participate in the development of allergic asthma in animals. However, whether Th17 immunity contributes to the systemically immune responses in allergic asthmatic patients is unclear.
Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from allergic asthmatics (n=29) and healthy controls (n=12). The frequencies of Th1, Th2 and Th17 cells were analyzed by flow cytometry. The related cytokines (IFN-γ, IL-4, IL-17, IL-22, IL-23 and IL-25) concentrations in plasma and culture supernatants were measured by enzyme-linked immunosorbent assay (ELISA) and Luminex. The level of retinoic acid-related orphan receptor γt (ROR γt), a key transcription factor controlling Th17 differentiation, was examined by real time quantitative polymerase chain reaction (RT-PCR).
Results: The percentages of Th2 and Th17 cells, the concentrations of Th2 and Th17 related cytokines were higher in allergic asthmatics than those in healthy controls; even some patients were treated with inhaled glucocorticoid. The percentages of Th17 cells, the plasma concentrations of IL-17 and IL-22 tended to enhance with the severity of the disease, while the IL-25 level was elevated in mild patients. A parallel elevation of IL-17 and IL-23 concentrations and the increase of ROR γt level were found in allergic asthmatics.
Conclusion: Our results suggest that besides predominant Th2 immunity, abnormal Th17 immunity may be also involved in the pathogenesis of allergic asthma.

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INTRA-ARTICULAR INJECTION OF HYALURONIC ACID INCREASES THE CD44 BEARING T CELLS IN OSTEOARTHRITIC JOINTS

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Methods: Fifteen patients with OA were included in the investigation. Peripheral blood mononuclear cells as well as synovial mononuclear cells were measured of their CD44 bearing condition by flow cytometry before and after HA injection in the knee joints.
Results: The peripheral blood mononuclear cells (PBMC) that bear CD44 molecule, an anchor protein of hyaluronan on the chondrocytes, were not significantly changed before and after HA injection (97.90±1.15% before *vs*. 97.73±1.14% after). Specifically, the peripheral blood CD3+ or CD4+ T cells bearing CD44 were also not significantly changed (65.02±10.47% *vs*. 61.77±9.90% for CD3+CD44+ cells; 42.44±9.58 *vs*. 45.03±8.95% for CD4+CD44+ cells). However, compared to that of the condition before HA injection, synovial fluid CD3+CD44+ cells were significantly increased in patients who underwent one course of HA intra-articular injection (10.99±7.96% before *vs*. 37.08±22.82% after, p=0.0128). On the other hand, synovial fluid CD4+CD44+ T cells were also not significantly changed (23.58±21.46% before *vs*. 20.19±15.86% after).
Conclusions: Intra-articular injection of HA into the osteoarthritic knee joint could

significantly increase the percentage of T cells that bear CD44 molecule in the synovial fluid while it would not modify the subpopulation of CD44 bearing CD4+ T cells in synovium as well as mononuclear cells with positive CD44 in peripheral venous blood. These results have suggested that HA may improve the cartilage metabolism in the synovial cavity in patients with OA.

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LAMP-2A AUTOANTIBODIES ARE NOT PREVALENT IN AN EASTERN US COHORT OF PATIENTS WITH ANTINEUTROPHIL CYTOPLASMIC AUTOANTIBODY (ANCA) GLOMERULONEPHRITIS

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The recent report by Kain *et al*. that autoantibodies reactive with LAMP-2 have a causal role in the pathogenesis of pauci-immune glomerulonephritis prompted clinicians and researchers to consider the efficacy of serological testing for these autoantibodies. This would be in conjunction with traditional testing for anti-PR3- and anti-MPO-ANCA. Before such steps are taken, the utility of these measures must be verified in independent cohorts of patients. We conducted a comprehensive serological evaluation for LAMP-2 autoantibodies in a USA cohort of patients with pauci-immune glomerulonephritis (n=104). ELISA assessment of reactivity against rLAMP-2 indicated 21% of samples were significantly higher than healthy controls (mean plus 2 SD) (p=0.004), far less than the 93% reported for the European patient cohort. LAMP-2 seropositive samples that were dually reactive with MPO were only positive for MPO by western blot analysis. In response to the reported analogy between the LAMP-2 antigenic-epitope and the E.coli protein FimH, we predicted that individuals generally healthy but who had E. coli urinary tract infections (UTI) (n=105) would exhibit seroreactivity against rLAMP2. Data indicate equivalent frequencies between the UTI controls and ANCA disease (p=0.97). Indirect immunoflourescence results were negative using rLAMP-2 overexpressing HEK cells and CHO-ldl cells, regardless of rLAMP-2 protein's post-translational glycosylation status. Lastly, we did not observe induction of crescentic glomerulonephritis in WKY rats injected with anti-LAMP-2 antibodies, as was previously reported. These data indicate LAMP-2 autoantibodies are not prevalent in our patient cohort and that MPO-ANCA and PR3-ANCA serological testing remains unsurpassed as diagnostic of disease.

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THE ROLE OF NANOPARTICLES IN CRYOGLOBULINEMIA: A PRELIMINARY STUDY

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Cryoglobulinemia refers to the presence in the blood of antibodies that precipitate, or clump together, under cold conditions. In spite of several past studies on cryoglobulins, no analyses were performed on Nanoparticles possible presence or role on cryoprecipitate. In this abstract, we present our results in the screening of 10 patients affected by membranous and proliferative glomerulonephritis, associated with hepatitis C infection. Peripheral blood specimens were obtained from the patients in vacuum tubes without clot activators for serum separation and in a sterile environment. Cryoglobulinemia was confirmed by the detection of protein precipitates in the serum maintained at 4°C during at least 7 days, which dissolved when heated at 37°C. A drop of three times washed cryoprecipitate, placed on a coverslip, was examined with a Quanta 200 ESEM FEG from FEI company, equipped with an EDAX Energy Dispersive X-ray (EDX) system for chemical analysis. Nanoparticles of Fe, Ni, Zn, Ti, Al and Si were found into IgG-IgM immune complexes. Interestingly Si Nanoparticles were observed in spherical shape coated by crioglobulins, while other Nanoparticles were observed mainly surrounded by immunoglobulins and not in spherical shape. Kidney biopsy samples coming from pathogenic tissues from all the patients were examined by FEG ESEM microscopy and showed correspondence among results. Confocal microscopy (TCS SP2, Leica Microsystems) immunofluorescence investigations using FITC-conjugated Goat anti-Human IgG+IgM (Jackson ImmunoResearch) on cryoprecipitate confirmed the presence of immunoglobulin complexes. Early results and Nanoparticles presence, strongly correlate with patients medical history, suggesting a possible role of Nanoparticles in crioglobulinemia.

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RANDOM PEPTIDE SEQUENCES RECOGNIZED BY ANTI-B2 GLYCOPROTEIN I ANTIBODIES

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Objectives: Studies concerning interactions between anti-β2glycoprotein I antibodies (anti-β2GPI) and β2glycoprotein I (β2GPI) suggest relevance of charge interactions and hydrogen bonds. However, epitope and paratope characteristics of clinically relevant (high avidity) anti-β2GPI, potentially useful in diagnostics and targeted therapy, still remain unclear.
The aim of our study was to determine epitope characteristics of various anti-β2-GPI IgG by phage display method.
Materials and methods: Monoclonal anti-β2-GPI IgG, purified polyclonal high avidity and low avidity anti-β2GPI IgG antibodies derived from plasma of APS patients were used to screen a linear heptamer phage display library (New England BioLabs, Ipswich, MA, USA). Single-stranded DNA from amplified selected phage clones was isolated and sequenced (MWG Biotech, Munich, Germany).
Results: We obtained a specific peptide sequence for each anti-β2GPI IgG antibody subgroup. High binding affinity of selected peptides was confirmed by ELISA. The selected peptides exhibited different ability (reaching up to 60%) to inhibit antibody-antigen interaction.
Conclusions: Selected peptides with high affinity for anti-β2GPI IgG antibodies represent putative amino acids in epitopes of purified high avidity and low avidity anti-β2GPI IgG antibodies and monoclonal anti-β2GPI IgG. Presence of hydroxyl and positively charged residues confirms the important role of hydrogen bonds and charge interactions in the binding of anti-β2GPI to antigen. With the decreasing antibody avidity the content of hydroxyl residues in selected peptides decreases and the content of positively charged residues increases, supporting the significance of hydrogen bonds for high affinity binding.

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UNDERSTANDING PATHOGENESIS OF ANCA: WERE ARE WE TODAY?

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ANCA are an useful tool for the diagnosis of small-vessel vasculitides (ANCA-associated vasculitides: AAV), such as Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome. There is strong circumstantial evidence that AAV are mediated through autoimmune responses, although direct evidence is lacking and indirect evidence is weak. Several clinical observations suggest an important role of ANCA in the pathogenesis of AAV: first, from all known ANCA specificities, only PR3-ANCA and MPO-ANCA are strongly associated with AAV; second, almost all ANCA-negative patients with limited WG do not progress to generalized disease (granulomatous and vasculitic lesions) unless they develop ANCA; third, vasculitic flares are rare without recurrence or persistence of ANCA; forth, there is a correlation between ANCA titres and disease activity in about two-thirds of patients; fifth, therapeutic interventions aimed to eliminate ANCA are effective treatments. However, the following evidence argue against a primary role of ANCA in the pathogenesis: first, if ANCA is essential to AAV, they should be present in all untreated patients, which is not the case; second, the strongest argument for ANCA not being essential is the observation that AAV patients can have active disease without ANCA; third, the levels of ANCA do not correlate well with disease activity in some cases. What is clear concerning the role of ANCA in AAV pathogenesis is that its presents is neither a necessary nor a sufficient condition for the development of vasculitis.

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THE EFFECT EVALUATION OF SOCIODEMOGRAPHIC, PSYCHOLOGIC, LABORATORY PARAMETERS AND LIFE STYLE HABITS ON THE LEVEL OF ANTINUCLEAR AND ANTI-DOUBLE-STRANDED-DNA ANTIBODIES

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Introduction: Systemic lupus erythematosus as a prototypic autoimmune disorder are characterized by autoantibody formation against nuclear antigens.

Purpose: To evaluate the relationship between antinuclear and anti-dsDNA antibody level with sociodemographic, psychological, laboratory, environmental factors, dietary, smoking and life style habits.
Methods: Comparison of 46 variables along with their intercorrelations was done in ANA-positive patients and ANA-negative healthy subjects.
Results: The average of ANA, anti-dsDNA and some other blood parameters was significantly different between patients and controls. Depression status and its prevalence in the patients were also higher than controls. Furthermore, more depressed patients had higher ANA and anti-dsDNA level which their level had a direct correlation with the age and weight of patients. However, ANA was more correlated with age and anti-dsDNA with weight. Higher ANA titer was associated with higher consumption of alcohol and permanent hair products which after controlling for age and weight, only the first correlation remained significant. Anti-dsDNA titer was positively associated with some of lifestyle habits which after controlling for age and weight, only correlations with hookah consumption and with sunlight exposure remained significant. Moreover the percentage of eosinophils was directly correlated with level of tow aforesaid autoantibodies.
Conclusion: These findings suggest that age, weight and depression score of ANA positive lupus patients along with some of health-related lifestyle habits such as hookah smoking, direct sunlight exposure and alcohol drinking may affect the titer of autoantibodies in these patients. Further studies are required to evaluate the role of these factors in the exacerbations of SLE.

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THE PREVALENCE OF THYROID DYSFUNCTION IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: To evaluate the prevalence of thyroid dysfunction and thyroid autoantibodies in Iranian patients with SLE.
Materials and methods: This was a case-controlled study being performed in Hafez hospital, a tertiary care center affiliated with Shiraz University of Medical Sciences, including a total of 88 patients diagnosed to have SLE and 88 age and sex-matched healthy volunteers as control group. Two study groups were compared regarding thyroid stimulating hormone (TSH), total triiodothyronine (T_3), total thyroxine (T_4), antinuclear antibody (ANA), antibodies to double-stranded DNA (dsDNA), anti- thyroglobulin antibody (anti-Tg) and anti-thyroid peroxidase (anti-TPO) antibody.
Result: The mean age of the SLE patients and controls was 32.16±9.19 and 32.48±9.47 years respectively (*p=0.821*). Patients had significantly higher prevalences (43.2% *vs*. 23.9%; *p=0.015*) and titers (221.8±570.5 *vs*. 78.2±277.2; *p=0.036*) of antibodies to Tg compared to controls. The patients had significantly lower titers of T_3 compared to controls (125.2±35.6 *vs*. 136.2±26.5; *p=0.021*). The titers of T_4 (7.63±2.1 *vs*. 8.19±1.82; *p=0.054*), TSH (3.38±3.2 *vs*. 3.3±5.2; *p=0.970*) and anti-TPO antibody (81.2±230.5 *vs*. 101.2±326.2; *p=0.638*) didn't differ significantly between two study groups.
Conclusion: Thyroid dysfunction was not higher in SLE patients compared to healthy individuals. However anti-Tg antibodies were higher in SLE patients. It has not yet been established that thyroid function tests should be performed routinely in SLE patients. However, testing anti-thyroid antibodies (ATA) in euthyroid SLE patients seems unjustified.

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IS ANTI-AQUAPORIN 4 A VALID MARKER OF NEUROMYELITIS OPTICA EVEN IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)?

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This is the case of a Caucasian twenty-six female patient affected by bilateral neuromyelitis optica (NMO) diagnosed in August 2009.
MRI brain and cervical spinal cord-dorsal such as lumbar puncture analysis were normal, showing a non demyelinating cause of disease.
She was initially treated with oral prednisone at the dose of 50 mg/day for one week; then she received a dose of 25 mg/day.
In December 2009 serum test showed mild leucopenia, ANA positive 1:1280 (homogeneous pattern) and autoantibody n-DNA positive (IIF and ELISA). In May 2010 the patient developed arthralgias so a diagnosis of SLE was performed according to ACR criteria.
In July 2010 neurological exam showed right optic deficit; a serological test for the NMO-IgG (anti-aquaporin-4) was performed and was positive (IIF). Azatioprine at the dose of 100 mg/day was suggested.
In Literature NMO-IgG has been recently described as a sensitive and specific markers for NMO; it is a demyelinating disease of the central nervous system characterized by severe episodes of optic nerve and spinal cord inflammation. Reports of an association between NMO and systemic autoimmune diseases were published, but the prognostic value of the antibody test in this case is uncertain. According to a single case described by Mehta et all in 2008, testing for NMO-IgG in cases of episodes of optic neuromyelitis associated to SLE may help clarify the diagnosis of a distinct disease process and an higher grade of disability, suggesting a more aggressive therapy.

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EVALUATION OF SOLUBE-LEPTIN-RECEPTOR CONCENTRATION AND ITS RELATIONSHIP WITH AUTOANTIBODY TITERS, PERSONAL, PSUCHOLOGICAL, LABORATORY AND LIFE STYLE PARAMETERS IN SYSTEMI-LUPUS-ERYTHEMATOSUS

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Introduction: Soluble-leptin-receptor (sLeptinR) may influences pro-inflammatory responses in some autoimmune disorders like systemic lupus erythematosus.
Purpose: To evaluate sLeptinR levels in lupus and its relationship with autoantibody titers, personal, laboratory and lifestyle indices.
Methods: 50 variables containing sociodemographic information, health-related lifestyle habits, depression and blood parameters besides the sLeptinR were evaluated in lupus patients and controls.
Results: Although there was no significant difference between weights, patients had significantly lower sLeptinR level after adjusting other variables. An inverse correlation was also found between weight and sLeptinR level in both groups. We showed that higher weight is associated with higher anti-dsDNA titer in patients. Furthermore only in patients, sLeptinR level had a negative correlation with ANA and anti-dsDNA titers and a positive correlation with the C3 level. Although, these relationships were not yet significant after adjusting for age and weight. Moreover, there was an inverse correlation between sLeptinR and contact with detergent or chemical solvents. However no significant differences in educational level, the rate of smoking or alcohol consumption, physical activity and dietary habits were found but depression status and its prevalence in patients was higher than controls. Patient's depression score was also negatively correlated with sLeptinR level. Our results do not support any other association between the level of sLeptinR in patients and other sociodemographic or blood parameters.
Conclusion: The negative correlation of serum sLeptinR and patient's weight or depression, together with its lower level in patients than in controls indicate that sLeptinR may play a role in pathogenesis of SLE.

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SEROLOGY OF RHEUMATOID ARTHRITIS: THE USEFULNESS OF ISOTYPE DETERMINATION IN THE CLINICAL ASSESSMENT

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Introduction: The 2010 Rheumatoid Arthritis (RA) Classification Criteria have enriched the serology with anti-citrullinated protein antibody (ACPA) besides Rheumatoid Factor (RF).
Methods: We considered 168 consecutive samples referred for ACPA determination with QUANTA Lite CCP3.1 IgG/IgA ELISA. We studied IgG and IgA ACPA using monospecific conjugates and IgG, IgM and IgA RF using QUANTA Lite ELISA panel tests. All materials were kindly provided by INOVA Diagnostics, USA.
Results: Seventy-eight samples (46%) were positive for IgG/IgA ACPA (see table). In 38 ACPA-positive early-RA patients, no association was found between IgA and clinical features. The two samples with single reactivity for IgA belonged to the group of 31 undifferentiated arthritis; in the same group, isolated IgG-RF was detected in one patient; no single IgA-RF was found. In 22 seronegative RA, IgG and/or IgA-RF was found in 9 (41%). Distribution and titre of ACPA IgA did not associate with that of IgA-RF in any group.

Table

78 samples positive for IgG/IgA ACPA	Both IgG and IgA positive	Only IgG positive	Only IgA positive	Both IgG and IgA negative
Low titre n=12 (15%)	0	8	2	2
High titre n=66 (85%)	40 (low IgA=18; high IgA=22)	26	0	0

Conclusions: ACPA IgA were detectable in about half of positive ACPA samples, mostly in combination with IgG at high level. Isolated ACPA IgA account for nearly 3% of positive results; clinical follow-up is warranted for assessing prognostic significance toward RA development. IgG and IgA-RF were common in seronegative RA, but not in undifferentiated arthritis.
Acknowledgments: The project has received a research funding from Schering Plough Immunology.

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INCIDENCE AND TIME OF RECOVERY OF PATIENTS WITH CELIAC DISEASE

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This study evaluates the time of recovery of the DC patients from the diagnosis to the recovery measured by the IgA antibodies TGt and AGA. Additionally, we examine the characteristics of the individuals that recovered, in particular whether different villous atrophy subtypes (3a-partial, 3b-subtotal, 3c-total) have different timings of recovery.
Methods: We studied 95 patients, diagnosed with DC from 2003 onwards, and that during 2009 tested IgA antibodies TGt and AGA in our lab. 33 were males and 62 females with the average age of 9.1years old. Patients from 17-24 years-old could not be included for lack of information on the diagnosis and information on whether gluten-free diet was followed. IgA antibodies TGt and AGA determination was done with the commercial enzyme-linked immunoassay (ELIA) produced by Phadia. Patient were considered recovered for values lower than 15 units.
Results: A multinomial logit shows that the 3b-subtotal subtype of the diseases was more common than 3a or the 3c subtypes among younger patients, and more likely than 3c in patients with high IgA antibodies TGt at time of the diagnosis. 41 recovered in average in 9.8 months. Of the 41 recovered patients, 53,2% and 83% had recovered after 9 and 12 months after diagnosis, respectively. Age, sex, different subtype of the disease (partial, subtotal and total) are not different between recovered and not recovered patients.
Conclusion: 43% of patients recovered in 9.8 months. 3b subtype is more likely among younger patients with high IgA antibodies TGt at time of the diagnosis.

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SILICA EXPOSURE AND ITS RELATION WITH THE APPEARANCE OF AUTOANTIBODIES

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Silica is ubiquitous in the environment as an abundant mineral and appears as an adjuvant to nonspecifically enhance the immune response and cause immunological abnormalities such as appearance of autoantibodies and autoimmune diseases. In the present study, a long-term evaluation of the presence of autoantibodies was undertaken in 130 silica-exposed workers compared to 98 controls. The individuals studied are workers occupationally exposed to free silica (SiO_2) for at least 1 year, independently of radiological abnormalities compatible with silicosis, including: miners, stonecutters, rock drillers as well as ceramic, metallurgic, foundry and quarry workers. We performed 3 evaluations of the production of antinuclear factor (ANF) and rheumatoid factor (RF) with a 2 year interval among them. Our results demonstrated an increase in the incidence of ANF and RF in 22% and 17%, respectively, of the exposed population, compared to 3% and 2%, in the control non-exposed group. In addition, 90% of the positive cases for ANF and 100% of the positive cases for RF, observed in the beginning of the study were confirmed in the two subsequent evaluations. New positive cases for ANF and RF appeared in the period between the evaluations, corresponding, respectively, to 6% and 3% of the population evaluated (n=120), whereas no new cases were found in the control group. These findings show important immune alterations in silica-exposed workers and reinforce the hypothesis that silica dust exposure may lead to autoimmunity.

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POST-TRANSLATIONAL MODIFICATIONS OF C1Q LEAD TO ANTIGENICITY AND BREAKDOWN OF IMMUNE TOLERANCE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: To determine how C1q breaks immune tolerance and affects SLE disease pathology.
Introduction: The autoimmune disease systemic lupus erythematosus (SLE) affects multiple organs in the body. The presence of anti-C1q antibodies is a major contributor to renal disease.
Results: Here we report that the A-B- and C-chain of C1q are susceptible to post-translational modification. The C-chain of C1q is particularly susceptible to modification by reactive oxygen species and granzyme B proteolysis and digestion. The remaining exposed A- and B-chain of C1q undergo further modification of specific amino acids in the globular head groups C1q creating neo-epitopes. The modified A-chain of C1q appears to be a specific target of anti-C1q antibody generation in SLE patients that may correlate with early SLE renal pathology. We have also demonstrated that specific reactive oxygen species (ROS) modifications also altered the bioactivity of C1q. Notably, ROS enhanced the ability of C1q to bind to immune complexes and enhanced proinflammatory complement activation. Peroxynitrite modification of C1q completely abolished the ability of C1q to clear apoptotic cells.
Conclusion: These findings explain in part why C1q becomes 'antigenic' and how such oxidative modifications can impair C1q's ability to resolve inflammation and target apoptotic cells for clearance.

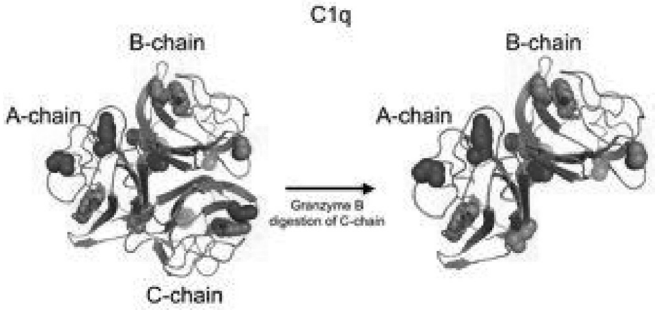

Fig. 1. The C-chain of C1q is susceptible to cleavage by granzyme B, exposing amino acids to ROS-mediated post-tranlational modification and anti-C1q production. (C1q digestion by granzyme B).

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IMMUNOCHEMICAL PROPERTIES OF CLINICALLY RELEVANT ANTI-B_2-GLYCOPROTEIN I ANTIBODIES

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Objectives: Significant morbidity and mortality present among patients clearly indicate the need to improve clinical risk assessment in antiphospholipid syndrome (APS). High avidity anti-β_2-glycoprotein I antibodies (anti-β_2GPI) correlate with thrombotic events in APS patients and could therefore represent the improved

prognostic marker. The aim of our study was to determine the unique binding characteristics of polyclonal high avidity anti-β_2GPI in comparison with low avidity anti-β_2GPI.
Material and methods: Surface plasmon resonance (SPR) was used to analyse interactions of polyclonal high and low avidity anti-β_2GPI IgG (derived from plasma of an APS patient) with β_2GPI. Influence of different binding conditions on interactions between respective antibodies and β_2GPI was studied by enzyme-linked immunosorbent assay (ELISA).
Results: SPR analysis showed that high avidity anti-β_2GPI formed larger amount of complexes with β_2GPI and exhibited slower dissociation from the β_2GPI under flow conditions than low avidity anti-β_2GPI. High avidity anti-β_2GPI displayed significantly higher affinity toward soluble β_2GPI and lower dependance on the antigen density than low avidity anti-β_2GPI, as revealed by ELISA.
Conclusions: Majority of high avidity anti-β_2GPI bound monovalently to β_2GPI and formed stronger immunocomplexes than low avidity anti-β_2GPI, among which bivalent binders prevailed. High avidity anti-β_2GPI were capable of binding soluble β_2GPI indicating either, their recognition of native epitopes or ability to induce a conformational change of β_2GPI exposing cryptic epitopes. Observed features are useful for the development of improved diagnostic methods capable of detecting clinically relevant (high avidity) anti-β_2GPI.

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PERFORMANCE OF THIRD GENERATION ANTI-CCP ASSAYS

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New generation anti-CCP ELISA assays have been developed for the more sensitive assessment of rheumatoid arthritis (RA).
We obtained serum samples from 119 consecutive patients with RA. For comparisons, we tested 118 control subjects, including 74 patients with other well-defined rheumatic diseases, such as 37 patients with primary Sjögren's syndrome (pSS), 30 with polymyositis or dermatomyositis (PM/DM) and 7 with osteoarthritis (OA), as well as 44 healthy subjects. We assessed IgM, IgA and IgG rheumatoid factor (RF), as well as anti-CCP using second (anti-CCP2) and third (anti-CCP3 and anti-CCP3.1) ELISAs.
In our hands (using either the manufacturer-suggested or the optimal cut-off), CCP3 ELISA performed better than CCP2, and CCP3.1 performed better than CCP3. The AUC values showing the diagnostic value of CCP2 and CCP3 tests are quite similar, while CCP3.1 ELISA represents a significant improvement. The quantitative anti-CCP3 and anti-CCP3.1 antibody levels are very much similar, almost identical, and even extremely high or low IgA levels do not seem to have much effect on them. When looking at the samples with non-identical anti-CCP3 and anti-CCP3.1 levels, again, we cannot predict the result based on IgA antibody titers. Anti-CCP3 negative specimens with very low anti-CCP IgA antibody levels are sometimes picked up by the anti-CCP3.1 ELISA.
In conclusion, based on the results of our in-house anti-CCP IgA test, isolated IgA positivity is extremely rare. Our results show that anti-CCP3.1 ELISA may be more sensitive in detecting IgG antibodies, too, compared to anti-CCP3.

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COMPLEMENT-MEDIATED REGULATION OF B-CELL FUNCTION - PHYSIOLOGICAL UPREGULATION OF CR1 AND FCΓRII ON MEMORY B CELLS IS LACKING IN SLE

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Immune complexes (IC) provide feedback signals for the immune system via FcγRs and complement receptors CR1 and CR2. Perturbations in the expression of these receptors that modulate BCR-mediated signals may lead to aberrant activation of autoreactive B cells. It is known that CR2 enhances, while CR1 inhibits BCR-induced activation (JI, 2002, 168, 2782.).
Here we show that the expression of CR1 and CR2 is regulated differentially during the development of human B cells. CR1 is up-regulated on memory ($CD27^+CD38^{low/-}$) B cells in contrast to the naïve ($CD27^-$) and germinal center ($CD27^+CD38^{high}$) subpopulations. We found that IgM^+ memory cells express more CR1 than their class-switched counterparts, while upon activation it is reduced. In sharp contrast, the appearance of CR2 remains stable.
Next we investigated the expression of the IC-binding receptors on various B-cell populations in SLE-patients. We found reduced expression of CR1 and FcγRII on CD27+ memory B cells and a disturbed ratio of naïve and memory B cells (53% versus 47%) as compared to healthy individuals (75% versus 25%). As activation strongly reduced CR1- and FcgRII expression and on tonsillar memory B cells, we investigated the influence of activation also on peripheral B cells. The expression levels of CR1 and FcgRII however, were similar both on resting and activated cells.
Based on these results we conclude that the decreased expression of CR1 and FcgRII on the memory B cells in SLE is not related to their activation status.

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NEUTROPENIA FOLLOWING INTRAVENOUS IMMUNOGLOBULIN (IVIG) THERAPY IN PEDIATRIC PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA

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Introduction: Children with idiopathic thrombocytopenic purpura (ITP) who are treated with intravenous immunoglobulin (IVIG) experience a decline in their absolute neutrophil count (ANC). The aim of this study was to investigate the incidence of neutropenia following IVIG therapy in children with ITP.
Methods: In this cross sectional study patients with ITP aged 1 to 18 years treated with IVIG referred to Ali-ashghar hospital for the period 2001-2007 without immunosuppressive diseases and who did not have a positive coombs test and also infection before the admission were included in the study and neutrophil count before, 1, 2, and 3 days after initiation of therapy was noted.
Results: Eighty nine patients entered into the study from whom 57.3% were male and 42.7% were female. Neutropenia after treatment was seen in 13(14.6%) of patients. But there weren't any statically significant difference between ANC before and 1, 2, and 3 days after the study. (p=0.922)
Conclusion: IVIG can lead to Neutropenia in a few numbers of patients which is transient and self limited and most of patients get benefits from IVIG therapy as induce platelets counts.

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ROLE OF THE RECEPTOR FOR THE GLOBULAR DOMAIN OF C1Q PROTEIN IN THE PATHOGENESIS OF CRYOGLOBULIN-RELATED VASCULAR DAMAGE

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Mixed cryoglobulinemia (MC) is a lymphoproliferative disorder observed in approximately 10 to 15% of hepatitis C virus (HCV)-infected patients. Circulating, non-enveloped HCV core protein is involved in the formation of cryoprecipitable immune complexes (ICs) and interacts with immunocytes through the receptor for the globular domain of C1q protein (gC1q-R). In this study we have evaluated serum gC1q-R levels in chronically HCV-infected patients, with and without MC. These levels were significantly higher in MC patients than in healthy controls and patients without MC, and paralleled specific mRNA expression in peripheral blood lymphocytes (PBL). It was also established that soluble gC1q-R circulates as a complexed form containing both C1q and HCV core proteins bound to IgM molecules with rheumatoid factor (RF) activity. Higher serum gC1qR levels negatively correlated with circulating concentrations of the C4d fragment, a split product of C4 complement component. The presence of sequestered C4d in the vascular bed of skin biopsies from MC patients was indicative of in situ complement activation. *In vitro* studies showed that release of soluble gC1q-R is regulated by HCV core-mediated inhibition of cell proliferation. A single mechanism that modulates its expression in PBL may thus be proposed. Our results indicate that upregulation of gC1qR expression is a distinctive feature of MC, and that dysregulated shedding of C1q-R molecules contributes to vascular cryoglobulin-induced damage via the classic complement-mediated pathway.

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POLYMORPHISMS IN RECEPTOR FOR FC OF IGG IIIA IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Ankylosing spondylitis is a chronic inflammatory disease considered as the mayor subtype of an inter-related group of rheumatic diseases called spondyloarthropathies. AS is of unknown aetiology, but genetic factors are involved. It has been

reported that receptors for the Fc of IgG (FcγR) play important roles in the initiation and regulation of many immunological and inflammatory processes, and genetic variants of FcγR have been associated with different autoimmune diseases. Considering that the biological activities of antibodies depend on the interaction of their Fc portion with effector system and the AS patients showed differences in the IgG subclasses produced to the 30 kDa band from *Salmonella typhimurium*. The aim of this study was to determine the 158-V/F polymorphism of FcγR IIIA to establish its possible association with AS. Thirty four patients with AS and 100 healthy subjects (HS) were included, and V/F polymorphisms of the FcγRIIIA were determined by using PCR. Resultants shown that 7/34 AS patients and 4/100 HS have the genotype V/V (OR=0.16; IC=0.44-0.58; *p*=0.0051), 17/34 AS patients and 48/100 healthy subjects shown the F/F haplotype (OR=0.92; IC=0.42-1.99; *p*=0.84) and 10/34 and 48/100 shown the V/F haplotype respectively (OR=2.2; IC=0.95-5.05; *p*=0.058). We propose that this polymorphism in FcγRIIIA could be associated with AS, but a higher number of patients and healthy subjects should be analyzed.

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IMPAIRED DEOXYRIBONUCLEASE I ACTIVITY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES

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Aim: To investigate serum DNaseI activity in patients with inflammatory bowel diseases (IBD).
Patients and methods: A cohort of 110 IBD patients was evaluated, aged 35±12 years, 77 with Crohn's disease (CD) and 33 with ulcerative colitis (UC), 69 females and 41 males. 50 SLE patients and 50 healthy blood donors were examined as control age-matched groups. Serum DNaseI activity was determined by ELISA (DNase Activity, Orgentec, Germany).
Results: Only 21 of 110 IBD patients (19%) had DNaseI activity above the reference cut-off value of 75%. DNaseI activity was significantly lower in IBD patients than in healthy controls and was higher in IBD patients than in SLE patients ($p<0.0001$ and $p<0.001$, respectively). Patients with UC exhibited higher DNaseI activity (74±19%) than CD patients (61±8%), $p=0.02$. DNaseI activity was significantly lower in female IBD patients (52±21%) than in male IBD patients (69±21%), $p=0.023$. DNaseI activity has shown a strong negative correlation with the serum concentrations of anti-nucleosomal antibodies in the autoimmune (SLE+IBD) cohort, as well as in the separate IBD cohort (both $p<0.0001$).
Conclusions: Reduced serum DNase 1 activity is characteristic of IBD patients, and DNaseI activity could be a useful parameter for the prediction of the formation of anti-nucleosomal autoantibodies in IBD patients.
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ASSOCIATION OF FC GAMMA RECEPTOR IIB WITH ANKYLOSING SPONDYLITIS

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Ankylosing spondylitis (AS) is the prototype of spondyloarthropathies, a group of inflammatory diseases with shared genetic background as well as common clinical features. Although the aetiology of the disease is unknown, environmental and genetic components have been implicated as predisposing factors. The family of Fc receptors for IgG (FcγRs) provides a prime example of how simultaneous triggering of activating and inhibitory signaling pathways sets thresholds for cell activation and thus generates a well-balanced immune response. Indeed, in a variety of human autoimmune diseases, such as arthritis and systemic lupus erythematosus, aberrant expression or the presence of allelic variants of FcγRs with altered functionality have been observed that contribute to the pathogenesis of these diseases. This study investigated the possible association of 131-R/H genotypes of FcγRIIB with AS. Genomic DNA was extracted from 23 AS patients and 85 healthy subjects. Polymorphism 131- H/R in the FcγRIIB was determined by using PCR. We found that 10/34 patients and 24/85 healthy subjects were H/H (OR=0.511; IC=0.198-1.31; *p*=0.163); Six out of 23 patients and 25/85 healthy subject were R/R (OR=1.18, IC=0.418-3.32; *p*=0.755) and 7/23 patients and 36/85 healthy subjects were H/R (OR=1.67; IC=0.625-4.454; p= 0.300). No significant association was found between polymorphism H/R in the FcγRIIB and AS.

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DEFECTIVE REGULATION OF NF-KB INCREASES THE ANTI-RO/SSA AUTOANTIBODIES-MEDIATED PRO-INFLAMMATORY CYTOKINES RELEASE IN SJÖGREN´S SYNDROME

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Sjögren's syndrome (SS), an autoimmune disorder and the second most common chronic systemic rheumatic disease, is characterized by a marked inflammatory infiltration of lymphocytes into salivary and lacrimal glands, which results in dry mouth and dry eye, and by the eventual total replacement of the acinar structure. IκBα is an essential regulator of the NF-κB transcription factor, which orchestrates the expression of a plethora of genes essential for controlling apoptosis, cell proliferation, and immune and inflammatory responses. Recent reports demonstrated that *IκBα* promoter polymorphisms are associated with susceptibility to SS. Here we focused on the hypothesis that NF-κB was involved in anti-Ro/SSA autoantibodies (Abs) (characterizing primary Sjögren's syndrome)-mediated inflammatory cytokine release from human salivary gland epithelial cells (SGEC) derived from healthy labial minor salivary gland biopsies. We also evaluated the potential physiological and therapeutic consequences of the induction of the NF-κB activation by expression of a dominant-negative mutant form of IkBα, which is resistant to phosphorylation and degradation. SGEC were transfected with the plasmide and the NF-κB activation was evaluated by flow cytometry, real time PCR, western blot. Immunohistochemistry was adopted to study the level of NF-κB activation on Sjögren´s syndrome biopsies. Our study demonstrated that anti-Ro/SSA Abs treatment determines a downregulation of IkBα gene in SGEC that increase pro-inflammatory cytokines release, confirmed by dominant-negative mutant form of IkBα transfection. These findings provide mechanistic insight into the development of Sjögren's Syndrome, and suggest the potential of NF-κB signaling as a therapeutic target for Sjögren's Syndrome and other autoimmune diseases.

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RECEPTOR FOR FC OF IGG TYPE IIIB AND ASSOCIATION WITH ANKYLOSING SPONDYLITIS

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Ankylosing spondylitis (AS) is a chronic inflammatory disease associated with immunogenetic and environmental factors and is thought to be of autoimmune nature. HLA-B27 is the most reported factor associated with AS, however AS is not a single gene disease and the genetic background of AS cannot be fully explained by association with MHC. On the other hand, autoimmune diseases has been associated with polymorphisms in molecules involved in the immune response such as CTLA-4, PD1 and polymorphisms in receptor for Fc of IgG(FcγR) as well. Polymorphisms in FcγR have a profound influence on human IgG binding; homozygosis for NA2/NA2 of FcγRIIIB lessens interaction with specific IgG subclass, and has been shown to be associated with lower phagocytosis capacity. We have previously report that AS patients shown an humoral immune response against the 30 kDa band from *Salmonella typhimurium* predominantly with IgG3 antibodies. The aim of this study was to analyze the NA1/NA2 polymorphisms of FcγRIIIB in AS patients and healthy subjects. DNA samples were obtained from 32 AS patients and 73 healthy subjects (HS). Polymorphisms in the FcγRIIIB were determined by using specific previously reported primers in a PCR protocol. Nine out of 32 AS patients and 10/73 HS have NA1/NA1 genotype (OR=0.404; IC=0.147-1.112; *p*=0.072), 12/32 AS patients and 31/73 HS have the NA2/NA2 genotype (OR=1.23; IC=0.418-3.32; *p*=0.634) and 11/32 AS patients and 32/73 HS were NA1/NA2 (OR=1.49; IC=0.625-1.32; *p*=0.364). No significant association was found between NA1 and NA2 of FcγRIIIB genotypes and AS.

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SYSTEMIC SCLEROSIS AND CHRONIC GVHD SCLERODERMA-LIKE HAVE OTHER SIMILAR PATHOGENETIC MECHANISMS THAN STIMULATORY AUTOANTIBODIES TO PDGFR?

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Chronic graft-versus-host disease (cGVHD) is a complex multisystem syndrome with overlapping features of immunodeficiency and several of the naturally occurring autoimmune diseases. In particular, scleroderma-like cGVHD may well resemble systemic sclerosis (SSc) in skin and lung involvement. Recent studies suggested that both these diseases are driven by stimulatory autoantibodies to PDGFR, which stimulates the production of reactive oxygen species and collagen by fibroblasts.
We studied 11 patients affected by SSc and 9 patients with scleroderma-like cGVHD to evaluate T-cell clonality in both diseases.
Clonality was assessed by analyzing the rearrangement of the TCRgamma gene. Additionally we investigated constitutive phosphorylation of ERK1/2 kinases. We analyzed also expression profiles of genes involved in apoptosis, including BCL2A1, CASP1, CASP6, EGR1, EGR2, FAS, FOS, TNF, TNFRSF1A, transduction signals (IKB, NFkB), intercellular adhesion (ICAM-1), and immune regulation (Fox-p3, CD52, CD83, CXCL1, CCL2, CCL5, IL-10, IL-17).
Ten patients (90.9%) with SSc and 5 patients (55.6%) with cGVHD had oligoclonal T-cell expansion. ERK-autophosphorylation was detected in 5 of 10 (50.0%) patients with SSc and in 2 of 5 (22.2%) patients affected by cGVHD. We also found that expression profiles of several genes implicated in the Th1/Tregs/Th17 responses were similar in patients with SSc or cGVHD, while expression profiles of genes associated with the Th2 response, were different.
In conclusion, we think that expanded clonal T-cells could play a critical role in the pathogenesis of both SSc and scleroderma-like cGVHD, probably by the activation of the same gene expression profiles and the same signal transduction pathways.

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IS SLEDAI OR SLAM SCALE A BETTER CORRELATE OF T CELL ACTIVATION IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS?

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Global disease activity measurement of systemic lupus erythematosus patients is important for clinical estimation and adjustment of therapy. The immune system activation plays a significant role in disease pathogenesis, with $CD4^+$ lymphocytes as central cells in specific immune response.
There is no information about relations between SLEDAI and SLAM activity scales and $CD4^+$ T cells activation measured at the same day, therefore we decided to check which of these scales better correlates with immunological changes in blood of SLE patients.
Samples of peripheral blood were obtained from 69 SLE patients with different disease activity assessed by two scales: SLEDAI and SLAM at the same day. Using flow cytometry we assessed the percentage of $CD4^+$ T cells with activation-associated receptors: CD69, CD95 and HLA-DR and $CD4^+$ T cells with killing properties containing perforin and granzyme B.
Obtained results have showed that the percentage of $CD4^+CD69^+$ cells did not correlated with neither SLEDAI nor SLAM scales. Significant and positive correlations were observed between percentages of $CD4^+CD95^+$ and $CD4^+HLA\text{-}DR^+$ lymphocytes and SLE activity, but only when activity was measured by SLAM scale, but not with SLEDAI scale. The percentage of $CD4^+perforin^+$ and $CD4^+$granzyme B^+ cells also strongly correlated with disease activity measured only with SLAM scale.
We conclude that SLE activity assessed by SLAM scale better reflects the ongoing changes of immune system activity of SLE patients than SLEDAI scale.

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DEPRESSION AS A CARDIOVASCULAR RISK FACTOR IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: The link between depression and cardiovascular diseases (CVD) in the general population is well established, but these studies have not assessed the state in patients with systemic lupus erythematosus (SLE). Objective of this study was to evaluate depression as a cardiovascular risk factor in patients with SLE.
Methods: We examined 84 consecutive patients with SLE who met ACR criteria in 1997. Age limits ranged from 18 to 69 years, mean age was 32.02±1.3 years. Depressive syndrome was evaluated by Hamilton Rating Scale for Depression (HRSD). Disease activity index was assessed by SLEDAI. Intima-media thickness (GIM) was detected by ultrasound examination of carotid artery. Lipid spectrum included determinations of total cholesterol, HDL-Ch), LDL-Ch and triglyceride levels.
Results: During the study identified 47 (55,9%) cases of depression where HRSD> 7. In 22 (26,2%) patients depression was weak (HRSD >7), in 23 (27,3%) - moderate (HRSD 17-24) and only in 2 (2,4%) patients was severe (HRSD> 25). Thickness of the GIM was established at 13 (36.1%) patients, ranging from 0,62-1,3 mm in patients with depression. Mean values of total CH (5.6 mmol/l) and LDL-Ch (3.3 mmol/l) were increased more marked in the group with depression. Among 47 patients with SLE and depression were detected 36 (42,8%) patients with cardiovascular diseases. SLEDAI index values ranged from 4 to 44 points (mean 20,03± 9.2).
Conclusions: Our results show the presence of depression in 55,9% patients with SLE. Depression has been associated with high activity and cardiovascular disease in LES in 22.6%.

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GENDER AND SCLERODERMA: DIAGNOSTIC UTILITY OF ANTI- RNAPOLY III

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Progressive systemic sclerosis (SSc) is an autoimmune disease that mainly affects women, with variations based on age and race. Anti-RNAP III antibody (ARA) are serological biomarkers highly discriminatory for a differential diagnosis and they may represent an index of severity of the disease.
In this study we evaluated, in a gender perspective, the ARA diagnostic utilities as early and specific biomarkers for disease.
A population of 145 patients, constisting of 95 cases of suspected SSc, 23 patients with suspected systemic lupus erythematosus (SLE) and 27 healthy donors, was tested for the presence of antinuclear antibodies (ANA) using indirect immunofluorescence (IFI) on Hep-2 substrate and for the presence of anti-RNAP III antibody through an immunoassay that uses RNA polymerase as recombinant antigen. Of 145 samples, 10 women of 92 resulted ARA-positive, with no LES suspicion, while 4 of 26 men tested resulted positive for anti-RNAP III, with only one case suspected of LES. None of the 27 control patients tested were positive using the ELISA test. The fluoroscopic ANA-IFI patterns of the ARA-positive patients resulted prevalently nucleolar and granular.
In this study it was possible to confirm the usefulness of ARA in the diagnosis of SSc, but it was also found that the biohumoral profile for ARA-positive patiences seems to be less discriminating in women than in men. Being SSc a disease that affects man and woman in a relationship equal to 10:1, a specific study, committed to create diagnostic profiles related to female gender autoimmune diseases, appears now clearly remarkable.

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JUVENILE DERMATOMYOSITIS - PECULIAR CLINICAL AND BIOLOGICAL ASPECTS

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Background: Juvenile dermatomyositis (JDM) is a multisystem disease of uncertain origin that results in nonsuppurative inflammation of striated muscle and skin.
Aims: We present a 10 years old boy diagnosed with dermatomyositis, presenting few peculiar clinical aspects both in the onset and the outcome of the disease.
Methods: The boy was admitted for the presence of violaceous discoloration of the eyelids with periorbital oedema and heliotrope malar rash, with no muscular complaints. Lab test did not proved a signicant inflammatory syndrome (ESR= 21mm/1h; CRP 1,89mg/L), but showed an important increasing of muscle enzyme levels: creatin kinase 6434 U/L, aspartate aminotransferase 340 U/L, lactic dehydrogenase 549 U/L. In the next days, other cutaneous changes appeared in turn, consisting in violaceous erythema of the lower limbs, subcutaneous oedema of the limbs, teleangiectasia, pruritic rash on the abdomen, swelling of the knees. After 3 weeks from the onset, muscle weakness and tenderness appeared, but first in the distal muscles of the lower limbs and, after another 2 weeks, in the proximal muscles. Electromyography demonstrated decreased amplitude and short duration of the potentials and muscle biopsy attested inflammatory changes. Myositis-specific antibodies (Anti-Jo-1, Anti-Mi-2) were negative.
Results: After starting therapy with oral Prednisone (1.5 mg/kg/day), the cutaneous abnormalities had a major improvement, the muscle enzyme levels significantly decreased. The outcome in the first three weeks of treatment was good, but long term prognosis is unclear.
Conclusions: Pediatricians should be aware of atypical manifestations of dermatomyositis in order to promptly diagnose and treat them.

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PLASMA LEVEL OF ANNEXIN A5 AND ANTI-ANNEXIN ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Aims: The purpose of the study was to assess plasma annexin A5 (ANX A5) and anti-annexin A5 (aANX A5) antibodies levels and to determine relationships between their concentrations and selected laboratory parameters in treated systemic lupus erythematosus (SLE) patients.
Methods: Levels of ANX A5 and aANX A5 antibodies were evaluated in 51 women with SLE. The results were compared between the total SLE group, subgroups on/without immunosuppressive therapy and the control (28 women). The relationships between ANX A5/ aANX A5 antibodies levels and laboratory variables (anticardiolipin antibodies-aCL, platelet count) were performed in the total SLE group and in the subgroups identified as the arithmetic mean of ANX A5 concentration in the control plus 1 to 4 standard deviations (SD).
Results: The whole SLE group and the subgroup on immunosuppressive therapy showed higher ANX A5 and IgG aANX A5 antibodies concentrations. A weak positive correlation was found between ANX A5 and platelet count, a moderate one between IgG and IgM aANX A5 antibodies in the whole SLE group. SLE subgroups with ANX A5 concentrations higher than the control mean plus 3 or 4 SD showed a weak/moderate negative correlation of this parameter with aANX A5 antibodies, moderate one with IgG aCL antibodies levels, moderate/high positive correlations with platelet count.
Conclusions: Elevated ANX A5 and IgG aANX A5 antibodies levels are associated with the severity of the disease. Depending on its concentration, ANX A5 correlates negatively with IgG aCL, IgG and IgM aANX A5 antibodies levels and positively with thrombocyte count.

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CONGENITAL HEART BLOCK WITH AND WITHOUT ANTI-RO/LA ANTIBODIES

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Background: Most cases of congenital heart block (CHB) detected *in utero* are associated with anti-Ro/La antibodies. Clinical features of negative cases are unknown.
Objective: To study anti-Ro/La-negative CHB detected *in utero* or at birth.
Methods: Forty-five consecutive fetuses with AV block were observed from 1990 to 2007 in 5 tertiary referral centers in Northern Italy. Anti-Ro/La antibodies were tested by ELISA, line-blot, counterimmunoelectrophoresis and immunoblotting.
Results: We observed 36 (80%) Ro/La-positive CHB versus 9 cases (20%) of anti-Ro/La-negative. Complete CHB were more frequent among anti-Ro/La positive mothers versus negative ones (94.44% vs 33.33%). All AV blocks were detected *in utero* in positive group while six (66.6%) in the negative mothers. Only two infants in positive group had an incomplete CHB: one reverted and one evolved in complete CHB after birth. In negative group six AV blocks were incomplete second-degree: 2 remained stable, 2 became complete after birth, 2 alternated with normal sinus rhythm that reverted in one patient. Pacemaker was implanted in 26 babies (72,22%) in positive group 4 of them died. Six (66,67%) were given pacemakers in negative ones. In positive group 2 fetuses died *in utero,* 4 were aborted, 3 had severe heart failure and died within 21 months after birth. Among negative fetuses two presented signs of heart failure *in utero* and 3 died (33.3%) shortly after birth.
Conclusion: Nine of the 45 consecutive CHB cases were anti-Ro/La-negative with no known cause. They were less stable and complete than the anti-Ro/La positive cases.

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LIPID PEROXIDATION AND ANTIOXIDANT ENZYMES IN HUNGARIAN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

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Introduction: It is proven that the release of toxic oxygen metabolism products causes tissue damage in different autoimmune diseases. Lipid peroxides have cytotoxic effects, whereas antioxidant enzymes can be protective mechanisms against the environmental stresses.
Aims of study: To evaluate the degree of lipid peroxidaton (oxidative stress) and the defective antioxidant enzyme system capacity in Hungarian patients with primary Sjögren´s syndrome(SS).
Patients and methods: Lipid peroxidation(LP) and antioxidant enzymes(superoxide dismutase=SOD, glutathione peroxidase=GP-ase, catalase=C-ase) and reduced glutathione(GSH) were measured from plasma and red blood cell(RBC) haemolysate by standard methods in 24 female patients with SS and in 37 healthy blood donors as controls. The results were compared between patients with different clinical manifestations. Pearson´s correlation coefficients and 2-tailed significance were calculated between the investigated parameters.
Results: In primary SS patients the lipid peroxidation of the plasma and RBC haemolysate and the superoxide dismutase activity of RBC did not change significantly but we observed a tendency for RBC LP elevation. Extremely high LP values were detected in 4 patients with vasculitis. The GSH and GP-ase activity of RBC and GSH level of the plasma increased, while the C-ase activity of the RBC haemolysate decreased significantly in SS patients as compared to the controls. Counting the Pearson´s correlation coefficients, a strong positive correlation was found between RBC GSH and GP-ase and SOD as well.
Conclusion: Oxidative stress may be an important pathogenetical factor in primary SS and targeting lipid peroxidation with dietary or pharmacological antioxidants can be regarded as an additional therapeutical tool.

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IS BUERGER'S DISEASE AN AUTOIMMUNE DISORDER?

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After a century, the puzzle of Buerger's disease (BD) has not yet been solved for the rheumatologists and the trigger of the disease is still controversial. There is not yet defined if BD is an autoimmune disorder, vascular hypersensitivity reaction, a pathogen-related syndrome or a kind of neurogenic inflammation. The table below is a list of causes and effects which may support each of these hypotheses.

Table. Hypotheses for Buerger's disease pathogenesis.

BD Hypothesis	Supportive findings	Non-supportive findings
Autoimmune disorder	1-linear deposition of antibody and complement along the elastic lamina. 2-Th1 immune response pattern in sub-acute phase of the disease 3- Serum anti collagen I,III antibody.	1- Non-destructive and segmental vascular involvement. 2-Normal ESR and acute phase reactant proteins in the absence of gangrene 3-uncommon visceral vessel involvement, 4-corticosteroids therapy is controversial.
Vascular hypersensitivity reaction	1-Strong relationship between tobacco consumption and outcome of the disease. 2-Occurrence of burning pain or thrombophlebitis migrans after tobacco smoke exposure.	Small number of all smokers around the world develops BD which is almost always in low socioeconomic class of the society.
A pathogen-related syndrome	1-Demonstration of oral bacteria in the thrombosis of occluded arteries.	1-Demonstration of oral bacteria in atherosclerosis and aortic aneurysm. 2-Small number of people with gingivitis develops BD.
Neurogenic inflammation	1-Low incidence of the disease in developed countries. 2-Disease occurrence in low socioeconomic societies and sometimes after a considerable stress; 3-Segmental small and medium-sized vessel, and neuro-vascular bandle involvement; 4-Circadian-like rhythm burning pain before the establishment of ischemia.	??????

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TUBULOINTERSTITIAL NEPHRITIS IN PRIMARY SJÖGREN´S SYNDROME

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Sjögren's syndrome is a progressive autoimmune disorder involving the exocrine glands, typically presenting with keratoconjunctivitis and xerostomia. It is characterized pathologically by a predominant lymphocytic infiltrate around epithelial ducts of exocrine glands on salivary gland biopsy.
However, several non-exocrine organ systems may also be involved, including skin, lung, gastrointestinal tract, central and peripheral nervous system, muscular skeletal apparatus and the kidney. Tubulointerstitial nephritis remains the most common presentation of renal involvement.
The authors present the case of a female patient of 48 years with complaints of xerostomia and xerophthalmia; the carried out tests showed anemia, sedimentation velocity of 71 mm, chronic renal failure, elevated rheumatoid factor, positive antinuclear antibodies (1/640), positive anti-SS-A (Ro) and salivary gland scintigraphy confirmed the diagnosis of primary Sjögren's syndrome. Due to the renal involvement it was performed a renal biopsy that confirmed the existence of chronic interstitial nephritis. By presenting this case, the authors intend to discuss the extra-glandular manifestations of this syndrome and therapeutic options for these cases.

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OVERLAP SYNDROME IN PAEDIATRIC PATIENTS: DOES IT FIT INTO THE MODEL?

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Background: Paediatric autoimmune connective tissue diseases (CTD) are rare with only small population reports on overlap or association.
Objective: To review overlap CTD in a paediatric series.
Methods: Of 82 cases fulfilling criteria for at least one CTD, followed over 10 years, 4 had overlap or associated syndromes. Clinical phenotypes and serological profiles were examined.
Results: All female,
1) 7y-old mosaic 7q1.2 chromosome deletion, development delay, presented dermatomyositis followed by linear scleroderma, high titres ANA, anti-DNA, Sm, but no clinical feature of lupus.
2) 8y-old had EMG proven-myositis preceded by chronic polyarthritis, Raynaud's, 'mechanic hands', interstitial lung disease and glomerulonephritis, high titres ANA.
Anti-DNA, RF and anti-Jo1, so anti-synthetase syndrome or lupus-myositis overlap were thought;
3) 9 y-old had typical Henoch Schönlein Purpura criteria except for prolonged rash that turned out to be morphea localised scleroderma over a year, but a negative serologic profile.
4) 13 y-old had a biopsy-proven diagnosis of autoimmune hepatitis (AIH) at the age of 6y, refractory to prednisone, cyclosporine A and azathioprine treatment, developed lupus features with rash and polyarthritis, fulfilling diagnosis with a typical serological profile during the last 3 years, Cases 1-3 were treated with prednisone and methotrexate, 2 with additional hydroxychloroquine and 4 is now on mycophenolate mofetil.
Conclusion: These overlap or associated features do not fit into the usual profile of adult overlap or undifferentiated connective tissue disease concerning localised scleroderma and vasculitis, posing many challenges as there are no evidence-based guidelines for treatment, only experience on dominant feature approach.

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SCLERODERMA HEART INVOLVEMENT: NON-INVASIVE ASSESSMENT OF PATHOPHYSIOLOGICAL MECHANISM AND ITS EFFECT ON PROGNOSIS

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We assessed cardiac involvement and prognosis in 22 consecutive patients (18 female, 4 men, aged 23-71) with Systemic Sclerosis, 8 diffuse, 14 limited; all had positive ANA results, 12 with ACA and 7 with anti-SCL-70 antibodies.
Patients underwent standard and Holter Ecg, Echocardiography; all performed cardiac MRI except for six patients (2 PM, 1 ICD and 3 sudden death); 4 underwent coronary angiography.
ECG showed LBBB in 3 patients**,** RBBB in 4, LAH in 3, second-degree AVB in 1, VT in 3, isorhythmic atrioventricular dissociation in 1, ventricular repolarization abnormalities in 7 (5 ischemic in origin) and Q waves in 1 patient receiving PTCA. Echocardiography showed diastolic dysfunction in 5, pulmonary hypertension in 4, pericardial effusion in 6, left atrial enlargement in 5, apical left ventricular dilatation in 1, left ventricle hypertrophy in 3. Septal dyskinesia was observed in the ICD patient, anterior dyskinesia in 2 with sudden death, septal and inferior wall hypokinesia in two non-fatal AMI. MRI found edema due to microcirculatory alterations in 3 cases, left ventricle segmental dyskinesia in 1 and outstanding mitral calcification in 1. FDG-PET showed viable hypoperfused myocardium in 1 patient with sudden death. Lung involvement was documented in 10 patients; isolated pulmonary hypertension in 2.
At the 5-years follow-up, 5 patients died, 2 had non-fatal AMI, 1 needed PM and 1 ICD.
We found high prevalence of cardiac involvement, high cardiac-related mortality and we defined clinical patterns significantly associated *($p<0.02$)* to major outcomes such as mortality, cardiac arrest, non-fatal AMI.

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AUTOANTIBODIES PROFILE AND LEVEL OF COMPLEMENT COMPONENT IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS IN SPLIT-DALMATIAN COUNTY

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Systemic lupus erythematosus (SLE) is a standard autoimmune disease marked by the whole spectrum of autoimmune antibodies. It is a multi-organic disease which mainly affects young women during childbearing years. The main biomarkers of the disease activity are the autoimmune antibodies and the complement.
The objective of this study was to check whether the titer of the certain autoimmune antibodies which are characteristic of lupus correlates with the complement component C3 and C4. We performed retrospective study and analyzed electronic register of SLE patients in Split-Dalmatian County in the period from 2005 to 2009 year. Mann-Whitney's test for testing the difference between analyzed variables was used for statistical analysis.
By the analysis of the electronic register of SLE patients in Split-Dalmatian county in the period from 2005 to 2009 year (130 patients), relation was observed between the presence of anti dsDNA and anti Sm antibodies and reduced values of C3 complement component. The positive correlation was determined between the presence of anti-histone (AHA) and anti Ro (SS-A) antibodies and reduced values of C4 complement component.
Among the examined group of 130 SLE patients who are treated in University hospital Split the significant correlation was established between C3 complement component and anti ds DNA and anti Sm antibodies. This is another confirmation that these antibodies are the main pathogen autoimmune antibodies in SLE. There is also an interesting correlation between C4 complement component and AHA and anti Ro antibodies, which shows the need for further research.

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AUTOANTIBODY DETECTION IN SERUM OF PATIENTS WITH AUTOIMMUNE MYOSITIS: IDENTIFICATION OF ANTI-SAE1/SAE2 ANTIBODIES BY UNLABELLED PROTEIN IMMUNOPRECIPITATION

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Myositis specific autoantibodies (MSA) are useful in the diagnosis of idiopathic inflammatory myopathies (IIM) and in the definition of disease subsets.
Objective: To develop a non radio-labelled protein immunoprecipitation (IP) technique for MSA identification in the serum of myositis patients, in order to identify antibody reactivity undetectable by routine methods.
Methods: Sera of 120 patients with connective tissue diseases (73 dermatomyositis, 37 polimyositis, 10 other connective tissue diseases) and 21 healthy controls were screened by a home-made procedure of non radio-labelled IP. In the same sera MSA and myositis associated antibodies were determined by immunoblotting and IP for RNA.
Results: Reference positive sera with known antibody reactivity were tested to evaluate the method's analytical specificity by unlabelled protein IP. Sera positive for anti-histidyl, anti-alanyl-tRNA synthetase, anti-Ro/SSA and anti-Ku immunoprecipitated the respective autoantigens, whereas sera from healthy controls did not immunoprecipitated any specific antigens.
Sera from five patients, affected with dermatomyositis (5/73=6,8%), immunoprecipitated two proteins of 40 and 90 kDa apparent molecular weights respectively, consistent with the subunits of the small ubiquitin like modifier activating enzyme heterodimer (SAE1/SAE2). The identity of putative SAE immunoprecipitated proteins was confirmed by immunoblotting on immunoprecipitates using commercial monospecific antibodies to SAE1 and SAE2.
Conclusion: Non radio-labelled protein IP is a specific analytical approach, more easily applicable than radio immunoprecipitation; it represents a more informative test than other routine investigations devoted to autoantibody profiling in autoimmune myositis. Using this method we succeeded to identify anti-SAE1/SAE2 antibodies.

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AN IMPAIRED ENDOTHELIAL DEPENDENT AND INDEPENDENT VASODILATION CHARACTERIZES THE MYO-ENDOTHELIAL DYSFUNCTION IN SSC PATIENTS

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Endothelial dysfunction is a marker of immune-mediated diseases and characterizes Systemic Sclerosis (SSc), and may be temporarily counteracted with an adequate pharmacological treatment, acting on the pathophysiological and metabolic changes, own of SSc. We evaluated 16normotensive SSc women, aged 49.8±16.1 years, 8 with limited and 8 with diffuse cutaneous SSc, symptomatic for Raynaud's phenomenon from 12.5±9 years, by measuring the endothelium-dependent, flow-mediated dilatation (FMD) and the endothelium-independent, nitroglycerin-mediated dilatation (NMD) of the brachial artery, compared with healthy controls. SSc patients showed an impaired FMD (4.4±6.7vs13.7±5.1, p<0.05), with poor differences between diffuse or limited SSc (3.1±2.3vs5.8±9.4, p=ns); abnormal values were recorded in 12 patients (75%), including 7 with diffuse cutaneous and 5 with limited SSc. The NMD was reduced (14.8±7.2vs17.9±3.4, p=ns), with abnormal responses in 4 cases, all of them showing an impaired FMD. The poor or absent endothelial-dependent and endothelial-independent vasodilation argue for an advanced vascular myo-endothelial damage, sometimes with an overt vasospasm during reactive hyperemia; these pathophysiological changes are likely involving the coronary arteries with an increased risk of silent or clinically overt ischemic heart disease. The observed myo-endothelial dysfunction is unrelated to the extension of skin disease or to a specific antibody pattern, is a marker of an advanced and irreversible vascular damage, with an increased risk for vascular complications and an unpredictable response to administered vasoactive drugs.

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SJÖGREN SYNDROME AND LIVER DISEASE IN CHILDHOOD: A CASE REPORT

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Aims: To describe the atypical onset of Sjögren syndrome (SS) in a female child confirming the heterogeneity at onset and highlighting the complexity concerning the early diagnosis of SS in childhood.
Methods: A 16 years old girl of caucasian origin has been followed up for abnormal liver function tests (AST, ALT, GGT) since the age of 3, without clinical evidence of liver disease. Common causes of hypertransaminasemia were excluded. CholangioPancreatography, Magnetic Resonance and Endoscopic Retrograde CholangioPancreatography were normal. The liver biopsy showed an unspecific picture of fibrosis without cholestatic liver damage.
Since the age of 12, she presented epigastric pain, dysphagia, inflammatory polyarthralgia, tallonitis, pruritus, xerostomy, xerophthalmia, Raynaud's phenomen.
Results: Biologic exams showed a high ESR and negative autoimmune serological markers. Esophagogastroduodenoscopy revealed esophagitis, whereas esophageal manometry and electrogastrography showed esophageal dysmotility and gastric dysrhythmia. Ocular sicca syndrome was confirmed by Shirmer test and tear film break up time (BUT); labial biopsy also revealed the presence of lymphoplasmocytic infiltration (grade 3 of Chisholm and Mason scale).
Conclusions: Diagnosis of SS was based on histological evidence of salivary gland involvement and she fulfilled the diagnostic adult criteria for SS. Primary Sjögren's Syndrome (SS) is characterized by autoimmune destruction of exocrine glands often extending to non-exocrine organs including the liver. Childhood SS is extremely rare and often has an insidious onset.
This case enphasizes the value of early diagnosis and underlines the usefulness of the validated criteria for a definite diagnosis.

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EVALUATING HAND IN SYSTEMIC SCLEROSIS

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Background: The hand arthropathy in Systemic sclerosis (SSc) could depend either on periarticular fibrosis or synovitis or even on an overlapping Rheumatoid arthritis (RA); though, the latter is a controversy in practice.
Objective: To define the clues when identifying nature of hand arthropaty in SSc.

Methods: In order to determine the hand arthropathy the serologic tests, hand radiology and other clinical features were assessed.
Results: Twenty eight consecutive SSc patients and 43 controls (21 Rheumatoid arthritis and 22 healthy controls) were included. Radiologic findings in SSc patients were: Erosions (25%), joint space narrowing (17.9%), arthritis (10.7%), radiologic demineralisation (42.9%), acro-osteolysis (25%), flexion contracture (28.6%) and calcinosis (17.9%). Anti-CCP antibody and RF positivity were as follows respectively: SSc group: 3 (11%) and 7 patients (%25); RA group: 23 (82%) and 19 patients (90.5%); healthy control group:1(4%) and 3 persons (13.6%).
Two patients (7.14%) were regarded as RA overlap, both had positive RF and anti-CCP positivity and their radiographies revealed arthritis. Seventeen patients (61%) were regarded as SSc arthropathy, all were negative for RF and anti-CCP but revealed nonarthritic radiological findings. (Among them, only one patient had positive anti CCP result). The remainder (9 patients) had no radiological or serological positive finding for arthropathy.
Conclusion: Hand involvement in SSc is a challenge in rheumatology practice; radiologic testing when evaluated with RF and anti-CCP will be a helpful tool to discriminate SSc arthropathy from RA-SSc overlap.

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PREGNANCY OUTCOME IN WOMEN AFFECTED WITH SLE NEPHRITIS

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Aim: Systemic lupus erythematosus (SLE) commonly affects women of childbearing age. Hypertension, anti-phospholipid syndrome and lupus nephritis are risk factors for adverse maternal/foetal outcome. This study was designed to examine pregnancy outcome in women with lupus nephritis.
Methods: Data were collected from 87 SLE patients between 2000 and 2010. Twenty-six women with nephropathy before pregnancy stated as the study group; 61 without renal involvement formed the control group.
Results: The groups were comparable for baseline charachteristics. Nephropatic patients had a mean creatinine level of 0.94±0.27mg/dl; 72% had proteinuria. Miscarriage percentage was 18% in the study group and 19% in the control group; foetal loss occurred once and twice, respectively. Preeclampsia occurred once in both groups, respectively, but HELLP was significantly more frequent in the study group (p<0.05).
Mean gestational age at delivery was lower (34w) than in the control group (38w), with a slightly higher incidence of caesarean sections (CS=60% vs 54%). IUGR percentage was 35% (mean percentile=36) in the study group versus 19% (p=0.02). Live birth rate resulted 86.9% in the study group versus 90.6%.
Nephropathy coexisting with phospholipid antibodies resulted in a higher percentage of miscarriage, HELLP, CS and lower foetal birthweight (mean: 27th percentile). Flares, CS, preeclampsia and HELLP were more frequent with associated hypertension.
Conclusions: SLE nephropathy significantly affects pregnancy: HELLP, IUGR and preterm delivery are more frequent when renal involvement is present. Antiphospholipid syndrome and hypertension raise the risk. Anyway, the percentage of live births is high (86.9%) and a positive outcome is possible.

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PATIENTS WITH ANTI-CENTROMER ANTIBODY IN PRIMARY SJOGREN'S SYNDROME

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Aim: Primary Sjögren's syndrome (PSS) is a chronic systemic autoimmune inflammatory disease characterized by the infiltration of the endocrine glands. ANA positivity and anti-SS-A, anti-SS-B and anti-Ro52 autoantibody positivity are common serological findings. In recent years, patients with positive anti-centromere are defined as a different group in PSS. We aimed in this study to investigate the frequency of the anti-centromere positivity in PSS and the effect of the clinical findings.
Methods: The study group consisted of 95 patients with PSS who were followed from KOU Rheumatology Outpatient Clinic between 2007-2010. All patients fulfilled the American-European classification criteria. The association between the anti-centromere positivity and clinical and laboratory findings was investigated with a standard form and the results were analyzed by SPSS 16.0.
Results: 8 PSS patients (8.6%) were positive for anti-centromere antibody. None of these patients had anti-SS-A, anti SS-B, anti-RNP antibodies (p=0.00 (Fischer's exact test)). In this group of the PSSpatients anti-CENP-B antibody positivity was significantly increased (p=0.000 (Fischer's exact test)). None of the patients with anti-centromer positivity had hypergammaglobulinemia, lymphadenopathy or cutaneous vasculitis. Pulmonary, neurological, locomotor system and gastrointestinal symptoms were not significantly different between the two groups of PSS patients. 1 out of 8 patients had lymphoma (maltoma). The only significant difference in all clinical signs was the Raynaud's phenomenon (p=0.025 (Fischer's exact test), OR: 5.79, CI: 1.267-26.46).
Conclusion: The anti-centromere antibody positivity in PSS may be associated with the Raynaud's phenomenon and the positivity of the CENP-B antibody.

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THE LIVER INVOLVEMENT IN ADULT ONSET STILL'S DISEASE

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Aim: Adult onset Still's disease (ASD) is a chronic systemic inflammatory disorder characterized by fever, dermatological findings, arthralgia/arthritis, leukocytosis and high ferritin levels. Liver abnormalities can be seen during the course of the disease, although these are not one of the main findings of ASD. We aimed to investigate the liver involvement in ASD patients.
Methods: The study group consisted of 26 patients (9 male and 17 female; mean age: 37.7±12.0 (19-66)) with ASD between 2007-2010. All patients fulfilled the Yamaguchi's classification criteria. The results were analyzed by SPSS 16.0.
Results: 13 patients (50%) had liver enzyme abnormalities. 11 patients (84.6%) had high SGOT and SGPT levels (mean SGOT: 133IU/L, mean SGPT 148IU/L). 8 patients (61.5%) had high cholestasis enzymes (mean GGT: 157IU/L, mean ALP 174IU/L). 6 patients had high levels of both liver and cholestasis enzymes. Only two patiens had isolated cholesatsis enzyme elevation. None of the patients had history for using alcohol or medications. Their viral and autoimmune serologies were negative. In radiological examinations (USG and for cholesatasis MR, MRCP) there were no findings out of hepatomegaly (30.8%). After 3 months of the steroid treatment, liver enzyme levels came to normal.
Conclusion: The liver enzyme level elevation may be more than expected in ASD. The cholestasis enzyme abnormalities may be seen without the radiological findings of cholestasis and may be reduced after treatment for ASD.

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MAY BETA GLUCAN TRIGGER AUTOIMMUNITY? SYSTEMIC LUPUS ERYTHEMATOSUS DEVELOPMENT AFTER BETA GLUCAN THERAPY

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Aim: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with unknown etiology. SLE is characterized by skin, kidney, liver, locomotor system, nervous system involvement. Some drugs may have role in the pathogenesis of SLE with triggering autoimmunity. Beta glucan is an immunomodulatory drug with immunostimulating effect and used frequently in primary care.With immunomodulator drugs associated autoimmunity have been reported previously, but there is no data about betaglucan. We report here a case of SLE developed after beta glucan therapy and presented with hepatitis and nephritis.
57-year-old male patient with hypertension and ischemic heart disease. At March 2010 he voluntarily started to use beta-glucan in order to strengthen the immune system. Since May 2010 the patient became fatigue and weight loss. Since increased fatigue after two months a laboratuary examination was performed. Bicytopenia (WBC: 2500/mm, lymphocyte: 700/mm, Hgb: 7.8g/dl), elevated liver enzymes (ALT: 748mg/dl, AST: 650 mg/dl), proteinuria (2600 mg/day) were investigated. He had no history of arthritis, photosensitivity, rash or fever. He had high titer of ANA and anti-ds DNA positivity. Viral and autoimmune hepatitis excluded after serological examination. Liver biopsy was observed minimal inflammatory infiltration, necrosis and occasional spot areas of macrovesicular steatosis in portal areas. Renal biopsy was showed diffuse proliferative lupus nephritis. After the immunesuppresive therapy liver enzyme and proteinuria levels returned to normal.
Conclusion: İnfectious diseases, some medications and herbal agents may trigger the development of SLE. The risk of autoimmunity development may increased by using of immunomodulatory drugs.

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TUMOR ASSOCIATED ANTIGENS IN SYSTEMIC SCLEROSIS PATIENTS WITH LUNG INVOVEMENT

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Objectives: An increase of some tumor associated antigens (TAAs) has been reported in interstitial lung diseases. The aim of our study was to evaluate the serum levels of some TAAs in patients with systemic sclerosis and interstitial lung involvement.
Methods: In 49 patients with systemic sclerosis and lung involvement, characterized by restrictive lung disease on pulmonary function test and/or by the presence of interstitial involvement on HRCT, the levels of CA15-3, CA19-9, carcinoembryonic antigen(CEA), CA125, Cyfra21-1, TPA and enolase were studied. The clinical and immunological characteristics of the patients, the FVC and DLCO were analyzed. In all patients any detectable malignancy was ruled out.
Results: 17(34.7%) patients presented an increase of at least one TAA. 18.4% presented an increase of CA19-9, 24.5% of CA15-3, 10.2% of CA125 and Cyfra21-1 and 8.2% of TPA. Only one patient presented an increase of CEA. 70.5% of these 17 SSc patients presented an increase of more than one TAA. SSc patients with an increase of TAAs presented lower FVC(72.2±16.0%) compared with SSc patients without TAAs increase(98.3±19.3%), $p<0.0001$. 76.5% of SSc patients with TAAs increase were positive for antiscl70 antibody with respect to 32.3% of the patients with antiscl70 but without TAAs increase, $p=0.004$. The levels of CA15-3, CEA and TPA inversely correlated with FVC (R=-0.05, $p<0.01$, for all correlations).
Conclusions: The concentration of more than one TAAs can be elevated in the sera of SSc patients with lung involvement. Furthermore, the increase of CA15-3 and CA19-9 seems to correlate with more severe lung involvement.

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ANTI-DNA ANTIBODY AVIDITY IN SLE

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SLE is a multiorgan autoimmune disease characterized by various antibodies formation. Low-avidity anti-dsDNA are a part of natural autoantibodies. One of possible events leading to SLE pathogenesis could be the high avidity anti-dsDNA synthesis. The target which is responsible for synthesis of pathogenic anti-DNA antibodies has not been clearly identified yet. Nucleosomes could be the possible one. Our aim was to prove the increasing antibodies avidity depending on the target antigen and to find a relationship between the tests reactivity, disease activity and disease duration.
Methods: Followed autoantibodies were analysed in 44 patients samples (National Institute of Rheumatic Diseases, Piešťany, Slovakia) with defined SLEDAI: anti-dsDNA CLIA (Bio-Rad,USA), anti-dsDNA-ELISA and high avidity anti-dsDNA-ELISA (Farrzyme, Binding Site,UK), anti-nucleosomes ELISA (Euroimmun,D), anti-dsDNA/NcX ELISA (Euroimmun,D). Avidity determination was done by elution-denaturating ELISA.
Results: Anti-DNA in SLEDAI groups show a slight increase. Anti-dsDNA ELISA avidity in SLEDAI groups showed weak dynamics. Relatively high avidity (60-71%) were set in anti-dsDNA ELISA. Anti-nucleosomal antibodies achieved lower avidity (34-48%). Significant correlation was found in Farrzyme and strong reactive anti-dsDNA CLIA. No significant difference was between anti-dsDNA antibodies reactivity and SLEDAI criteria frequency. Surprisingly, there was no difference between SLEDAI immunological criteria frequencies depending on disease duration.
Conclusion: We failed to prove assumption of differences in anti-dsDNA antibodies maturation detected by "classical" ELISA test and "high avidity" Farrzyme test. Over the last two decades a number of publications was devoted to this problem and still has not been found a solution explaining the role of autoantibodies in SLE pathogenesis.

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ANTIPHOSPHOLIPID ANTIBODIES (APLAS) AND TAKAYASU ARTERITIS (TA) - A CASE REPORT

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A 27-year-old woman developed Raynaud s phenomenon, claudication of both upper extremities and visual disturbances. The complains started during the last 3 months of her the only pregnancy and she delivered a healthy child. Two years later she presented at hospital with absence of radial and brachial pulses in upper extremities and vascular bruits over the right carotid and both subclavian arteries (SCA). Femoral and dorsum pedis pulses were palpable. Blood pressure was 160/95 mm Hg on both legs. Angiography: occlusion of common carotid artery (ACC) and left SCA, circular narrowing of the right ACC and narrowing of the right SCA to the origin of vertebral arteries (VA). Collateral circulation with retrograde flow through the left VA to the left SCA.
C3 and C4 levels were normal. Immunological parameters were negative except positive lupus anticoagulant and anticardiolipin antibodies (aCLa) in two subsequent measurements.
The diagnosis of TA - type III according to Ishisawa relied on her clinical data meeting all ACR 1990 criteria.
Therapy included methylprednisololone, cyclophosphamide and methotrexate. Ethylbuscomate was given for positive LAC and aCL antibodies although there was no manifest thrombosis. In the course of therapy, a moderate improvement of carotid flow occurred. Month later, at home, the patient had epileptic attack and died. Autopsy was not performed.
Only a small number of APLAs positive TA patients (all with severe course of disease) have been described. These data indicate that APLAs might contribute to the pathogenesis of TA aggravating vasculopathy increasing the severity of the disease.

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SUDDEN CARDIAC DEATH AND AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Introduction: Despite its importance, the autonomic nervous system (ANS) dysfunction is rarely studied in patients with systemic lupus erythematosus (SLE).
Objective: The aim of this study was to analyze predicting factors of sudden cardiac death associated with ANS dysfunction degree in SLE patients.
Method: The cardiovascular autonomic function was assessed in 52 patients (46 women and 6 men) with SLE in the study group and 41 healthy subjects (23 men and 17 women) in the control group. Despite the less sensitive tests for cardiovascular autonomic reflexes that are commonly applied in the previous studies, we used a comprehensive and extensive tests for ANS function assessment, including short-and long-term heart rate variability with non-linear analysis (Poincare diagram) as well as QT interval analysis.
Results: All of the cardiovascular reflex test results indicated that a heart rate disorders were more common in patients than in healthy controls. In the majority of SLE patients, we found the typical form of Poincare diagram as a point that indicated serious autonomic function disorders and poor prognosis. Predicting risk for sudden cardiac death associated with ANS dysfunction, revealed a statistically significant decrease in heart rate variability, depressed triangular index of 42.5±12.4, the presence of supraventricular arrhythmias, prolonged QTc interval (442±28.6 ms) and the punctuated form of Poincare diagram (24.4%).
Conclusion: The increased risk of sudden cardiac death in SLE patients is associated with severely impaired ANS function, and the sympathetic predominance and hyperactivity, which leads to the lethal arrhythmia occurrence.

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THE PREVALENCE OF AUTOANTIBODIES AGAINST NUCLEAR ANTIGENS IN PATIENTS WITH RHEUMATIC DISEASES

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Objective: The aim of this study was to assess the frequency of antibodies against nuclear antigens in patients with rheumatic diseases and to detect the association of these antibodies with inflammatory markers - C reactive protein (CRP) and rheumatoid factor (RF).
Materials and methods: The analysis involved sera from 50 patients (47 female and 3 male) with rheumatic diseases: mixed connective tissue diseases (n=26), systemic lupus erythematosus (n=8), Sjögren syndrome (n=8), scleroderma (n=8). Sera from all patients were positive for antinuclear antibodies (ANA) by indirect immunofluorescence method (Hep-2 cells, ImmcoDiagnostics, USA). The specificity of these antibodies to different nuclear antigens was detected by immunoblotting method (ANA profile 3 Euroline, Euroimmun, Germany). RF and CRP concentrations were assessed by nephelometry (BNII nephelometer, Dade Bering, Germany).

Results: We detected antibodies to Ro-52 in 56% of patients, anti-SS-A-44%, anti-SS-B-26%, anti-ds-DNA and anti-nukleosomes antibodies-24%, anti-nRNP/Sm, anti-Scl-70 and antibodies to histones-14% of patients. Antibodies to Jo-1, CENP-B, PCNA, ribosomal P- Prot antigens were detected not so frequently as 10% of patients. There were estimated, that the highest CRP level was associated with antibodies to Scl-70 and highest RF level was in conjunction with antibodies to SS-B.
Conclusion: We defined that antibodies to Ro-52/SS-A antigens are the most frequently detectable in autoimmune rheumatic diseases, but there wasn't established association of these antibodies with inflammatory markers.

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DISEASE ACTIVITY PATTERNS IN A COHORT OF ITALIAN PATIENTS WITH SLE: A SEVEN-YEAR FOLLOW-UP STUDY

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Aim: To evaluate disease activity patterns and flare occurrence in SLE patients.
Methods: We used our Lupus Database which included 487 SLE patients, recruited between 1970 and 2008. Patients diagnosed with SLE before 2004 and seen, at least every six months, from 2004 to 2010 were considered. Disease activity patterns were defined using SLE Disease Activity Index (SLEDAI) score, as follows: *serological active, clinically quiescent disease* (SACQD), SLEDAI=0, excluding serology, in patients taking hydroxychloroquine and prednisone ≤5 mg/day; *chronic active disease* (CAD), persistent disease activity over time (SLEDAI≥6 for at least ≥1 year); *relapsing-remitting disease* (RRD), periods of disease activity interspersed with periods of inactivity (SLEDAI=0, excluding serology). Flare was defined as SLEDAI ≥4 from the previous visit, excluding serology.
Results: 135 consecutive patients, out of 356 diagnosed between 1970-2004, were evaluated. Ninety (68.9%) patients fulfilled inclusion criteria: 35 (38.9%) with SACQD, 29 (32.2%) with CAD, and 26 (28.8%) with RRD. Sex, disease duration, time from disease onset to diagnosis, and type of flares were similar among groups. The number of patients treated with immunosuppressants was higher in CAD compared with RRD group (25 vs 17, p=0.042). Mean±SD number of flares was higher in CAD compared with RRD group (2.64±1.25 vs 1.66±0.87, p<0.01). Thirty-six (40%) patients experienced >1 flare; the annual flare rate in CAD and RRD groups were 0.37 and 0.21, respectively.
Conclusion: Two-third of patients in this SLE cohort experienced active disease; patients with CAD, despite a more aggressive therapy, are at higher risk of developing flares.

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EVALUATION OF A EVIDENCE BASED CLINICAL PATHWAY FOR SYSTEMIC RHEUMATIC DISEASES

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Objective: To describe our experience with a clinical pathway (CP) specifically structured for systemic rheumatic diseases.
Methods: We reviewed the medical record of 368 consecutive subjects that were admitted in our Internal Medicine Department in two consecutive years (2008-9). Data related to subjects, diagnoses and stay were collected. A semi-structured questionnaire investigated the patients' and staff (physicians and nurses) perceptions and suggestions.
Results: Our experience started in January 2000. Since then, more than 1000 subjects have been followed by means of our clinical pathway (CP) specifically planned for subjects with systemic rheumatic diseases. Main diagnoses were systemic sclerosis (25%), Sjögren's syndrome (20%), rheumatoid arthritis (18%) and systemic lupus erythematosus (15%). The mean hospital stay was significantly reduced from 8.8 to 4.2 days. The patients' questionnaire revealed their approval for the general organisation of the stay, the reduced stay in the hospital and the communication with personnel. The staff's questionnaire documented major opportunities to communicate among the multiple care providers usually following these subjects and the increased workload necessary to organise and follow the CP. Finally, we documented an improved compliance with the recognised national and international guidelines.
Conclusions: Our study shed some light onto efficacy, cost-effectiveness and cost-profit balance of a CP specific for subjects with systemic rheumatic disease. Strategies to improve efficacy and cost-effectiveness are discussed. Moreover, patients referred satisfaction for their stay, mainly due to a positive interaction with the staff and to the complete information provided.

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HYPERGAMMAGLOBULINEMIA: A MARKER OF DISEASE ACTIVITY IN MIXED CONNECTIVE TISSUE DISEASE?

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Background: Mixed connective tissue disease does not have a defined disease activity criterion, except for the one based on corticosteroid dose (Burdt *et al*. 1999).
Purpose: The aim of this study was to determine if gammaglobulin levels have a diagnostic utility as marker of disease activity in MCTD.
Methods: Data from 104 MCTD patients (Kasukawa's criteria) with a follow-up of at least 3 years were obtained. Gammaglobulin levels were measured by protein electrophoresis. Disease activity was defined according to Burdt *et al*. (1999).
Results: Mean age was 34.5 years (13-61), 97% female and the mean disease duration was 167.5 months (23-480). Forty-four patients (42.3%) were active and 60 (57.6%) were inactive. Regarding therapy, 45.7% were under prednisone and 60.3% were taking immunosuppressors. Patients with gammaglobulin levels ≥2.5g/dL were more frequently observed in active patients compared to the inactive group (11% vs. 8%, p=0.03) in spite of a similar mean gammaglobulin level in both groups. In addition, patients with gammaglobulin levels ≥2.5g/dL had more lung fibrosis than those with lower levels (20.9% vs. 8.06%, p=0.046). Of note, longitudinal analysis revealed that disease activity was associated to an increase of at least 0.3g/dL in gammaglobulin levels (OR: 2.06, CI 95%: 1.28-3.31, p=0.002) with specificity of 87.7%, even if the levels were lower than 2.5g/dL.
Conclusion: We have demonstrated for the first time that gammaglobulin levels and/or their increase are possible valuable markers of MCTD disease activity reinforcing the role of B-cell hyperreactivity in this disease.

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MCTD: A COHORT OF 118 PATIENTS

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MCTD (Mixed Connective Tissue Disease) is an autoimmune rheumatic disease with anti-RNP antibody in high titers as a decisive marker. Its incidence is approximately 1/10,000. As MCTD is rare and there are few studies characterizing it in a regularly followed population we aimed to report a large series of such patients.
Methods: Records of 118 MCTD outpatients of a tertiary Hospital in São Paulo - Brazil, were reviewed and included in a database. Kasukawa's criteria (1987) was used for diagnosis and persistent negative anti-dsDNA and anti-Sm antibodies were mandatory. Data included demographic, clinical, laboratory and image information. Associated Sjogren´s syndrome was also recorded.
Results: We observed a large female predominance (95%); 64.4% were Caucasian. The average age of onset was 33.9 years (range 13-61). Anti-RNP titer varied from 1:1,000 to 1:512,000 with an average of 1:55,891. Raynaud's phenomenon was very prevalent, in 97.4% of patients, higher than puffy hands (78.8%). Cardio-pulmonary compromise was found in 97.4% of the total, including 74.6% of interstitial lung disease and only 5.0% of myocardial compromise. Serositis was diagnosed in 17.8% of the patients, including one myocardial tamponade. Esophageal involvement was very prevalent (81.3%) and only half of the group had myositis (55.9%). Sjogren's syndrome was present in 30% of patients. SD pattern in nailfold capillary microscopy was found in 67.0% of them. MCTD is a rare syndrome and many aspects are to be studied and described. We reported here a large number of patients, with clinical and laboratory characteristics.

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THE SENSE OF SMELL IN POLYMYOSITIS AND DERMATOMYOSITIS

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Our aim was to analyze the sense of smell in patients affected with polymyositis-dermatomyositis (PDM)
We performed a case-control study on 40 patients with PDM (34 female, 6 male; mean age 54±13 years, range 30-73) and 40 healthy subjects, selected by the best friend method, matched for age, sex, and life-style, as controls. The olfactory func-

tions were analyzed by a "Sniffin' Sticks test". The test result is expressed with a score (TDI) which distinguishes normosmia (TDI>30), hyposmia (TDI 15-30), and anosmia (TDI< 15). Mood was investigated with Beck Depression Inventory test (BDI). The statistical analysis was performed using Fisher test, Student T-test and Person correlation.
TDI was significantly reduced in patients compared to controls (26.47±5.57 vs. 30.03±3.83 (p<0.001). Hyposmia was detected in 29 patients (72.5 %), anosmia in 2 (5 %), and normosmia in 9 (22.5 %). Considering the entire group (80 subjects) an inverse correlation of TDI score with age (r=-0.360, p=0.001) and BDI (r=-0.383, p<0.001) was observed. Considering only the group of patients, the TDI score was lower in individuals ≥45 years of age compared to those <45 years. (25.53±6.29 vs. 28.67±2.31; p=0.027) and in depressed compared to non-depressed patients (25.66±5.91 vs. 29.69±1.90; p=0.037); in addition, the inverse correlations with age (r=-0.367, p=0.020) and mood disorders (r=-0.339, p=0.032) were confirmed. Finally, a negative correlation with corticosteroid dosage was found (r=-0.354, p=0.025).
Patients affected with PDM had a significant reduction in the sense of smell, which is inversely correlated with age, BDI and corticosteroid therapy.

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ASSOCIATION OF ARTHRITIS AND OTHER IMMUNE-MEDIATED DISORDERS WITH PERIODONTAL DISEASE AMONGST A COHORT OF PERIODONTAL PATIENTS

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Introduction: There are similarities in the pathogeneses of periodontitis (PD), arthritis and other immune mediated disorders such as allergies, eczema and psoriasis. Mechanisms that drive an antigen-mediated inflammatory response and sequelae of oxidative stress-induced tissue damage result from a poorly modulated immune response.
Objective: Identify the prevalence of arthritis(A); allergies, eczema and psoriasis (B) amongst periodontal patients for correlation with periodontal disease severity.
Methods: A cohort of 475 referred patients were examined for clinical and radiographic parameters of periodontal disease. Diagnosis based on the proportion of bone support categorized patients with early, moderate and severe PD. This was correlated with A and B.
Results: Group A comprised 11% of the cohort; 81% presented with severe- and 19% with early/moderate PD.
Mean number of teeth lost was similar within this group; 80% of this group were >50y.
Group B comprised 18% of the cohort; 80% of this group presented with severe periodontitis and a 2-fold increase in tooth loss over early/moderate PD; 60% of this group were <50y.
Greater mean age of arthritic patients could account for a similar prevalence of tooth loss; considering the significant association of age with tooth loss: p<0.0001 for 50 plus subjects, when compared with <30y olds. Confirmation of observed differences in prevalence of severe periodontal disease between those with or without A and B calls for increased power.
Conclusion: Severe periodontitis correlated with both arthritis and other immune mediated conditions studied. A reduced inflammatory burden following treatment of PD could potentially improve these conditions.

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DYSEXECUTIVE SYNDROME; A SPESIFIC PATTERN OF COGNITIVE IMPAIREMENT IN SYSTEMIC SCLEROSIS

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Background and aim: Systemic sclerosis (SSc) is a connective tissue disorder that is characterized by microvascular damage and tissue fibrosis. Although nervous system involvement is unusual in SSc, cerebral hypoperfusion has been shown in imaging studies. Here, we aimed to evaluate cognitive functions in SSc patients who had no previous or current history of neurological involvement.
Methods: Thirty-one scleroderma patients were examined. Fifteen rheumatoid arthritis patients (RA) and 20 healthy subjects (HC) were selected as age and sex-matched controls. For the purpose of assessing different domains of cognition we designed a brief, but comprehensive neuropsychological test battery.
Results: Most of the executive measures (Wisconsin Card Sorting Test [WSCT] number of categories, number of perseverative responses, percentage of perseverative errors, percentage of conceptual level responses and California Verbal Learning Test [CVLT] number of perseverations) were significantly worse in Ssc patients as compared to both RA patients and HC subjects (p<0.05). On the other hand, measures of attention and memory (Wechsler Memory Scale-3rd Revision-Digit Span Subtest [WMS-III-DS], Stroop interference Test, verbal fluency measures and several learning and recall measures of CVLT), seemed to be better (p<.005) in HC group as compared to both patient groups.
Conclusion: This is the first study showing a specific pattern of cognitive impairment in a relatively large sample of SSc patients. Our findings suggest that a dysexecutive syndrome might be specific to the cognitive impairment in SSc. whereas attentional and memory problems might arise from other confounders such as disease duration and chronic drug use.

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RETROSPECTIVE INVESTIGATION OF PATIENTS WITH NEUROPSYCHIATRIC (NP) MANIFESTATIONS IN A LUPUS CLINIC

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Background: Neuropsychiatric manifestations are common in patients with Systemic Lupus Erythematosus. This study reviews neurological and psychiatric manifestations in Lupus Clinic at Central Middlesex Hospital from 1996 - 2010.
Method: Retrospective audit of notes of 52 patients with NP manifestations.
Results: 49 female and 3 male patients aged 22-89 years. 50 patients with SLE (9 SLE/Sjogren's) and 1 with Primary Sjogren's. One had paraparesis and cerebral ischemia with HTLV I positive serology and was excluded from this study.
Discussion: 18 patients had NP within the first year of diagnosis of SLE. 25 patients had more than one NP manifestation. The manifestation ranged from mild to moderate cognitive dysfunction (20), persistent headache (14), mood disorders (9), seizure disorders (2), PRES (1),epilepsy (1), psychosis (2), acute schizophrenia (2), organic brain syndrome (2),peripheral neuropathy (3) ,paraparesis (3), hemiparesis (2), acute confusional state (2), mononeuritis complex (1), cranial nerve palsy (1), longitudinal myelitis (2), sensory motor axonal polyneuropathy (1), truncal ataxia (1), behavioural problems (1). Serology showed 8 APL positive, 3 Antineuronal (Anti-Ma2/Ta), 1 Anti-NMDA1Receptor, 1 Ribosomal P. 30 had abnormal MRI, predominantly vasculitic and ischemic changes. 29 had EEG. 18 of 33 showed matched Serum /CSF Oligoclonal bands. 31 had Neuropsychiatric Assessments. 23 had steroids orally or intravenously, 17 had Cyclophosphamide intravenously. Update on generally stable functional outcomes in most cases. One mortality followed respiratory failure and multi-organ damage, 2 recalcitrant headaches,1 still agoraphobic, 1 relapse post infection required ventilation, 1 poor result following NMDA1R syndrome,1 poor outcome of longitudinal myelitis.

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A RARE CASE OF CHEST PAIN INDUCED BY TAKAYASU'S ARTERITIS MIMICKING ACUTE AORTIC DISEASE

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Takayasu's arteritis (TA) is a rare idiopathic vasculitis typically presenting with non-specific systemic signs and symptoms such as arthralgia, fever, fatigue, headaches, rashes and weight loss. We describe the case of a patient with non specific clinical symptoms of TA at presentation revealing the importance of imaging modalities for earlier diagnosis and therapy.
A 56 year-old women was referred to our Hospital for a intermittent chest pain perceived as pressure-like in quality without dyspnea, fatigue, arthralgias, fever and a weight loss of 5 Kg. Laboratory abnormalities consisted of anemia, increased indices of inflammation and hypergammaglobulinemia. A echocardiographic study showed areas of crescentic thickening and diffuse echolucency of ascending aorta and arch suggestive of a diffuse inflammation. A minimal pericardial effusion was detected. In suspicion of TA was performed a PET. This imaging technique showed an inflammation of the wall of the aorta and its major branches including subclavian, iliac and femoral arteries (Fig. 1). Diagnosis of early TA was performed. The patient received oral prednisolone (1 mg/Kg/day) tapered to 5-10 mg/day in two months. After three months the patient was asymptomatic, echocardiographic study and another PET did not show inflammation of the aorta and its branches.

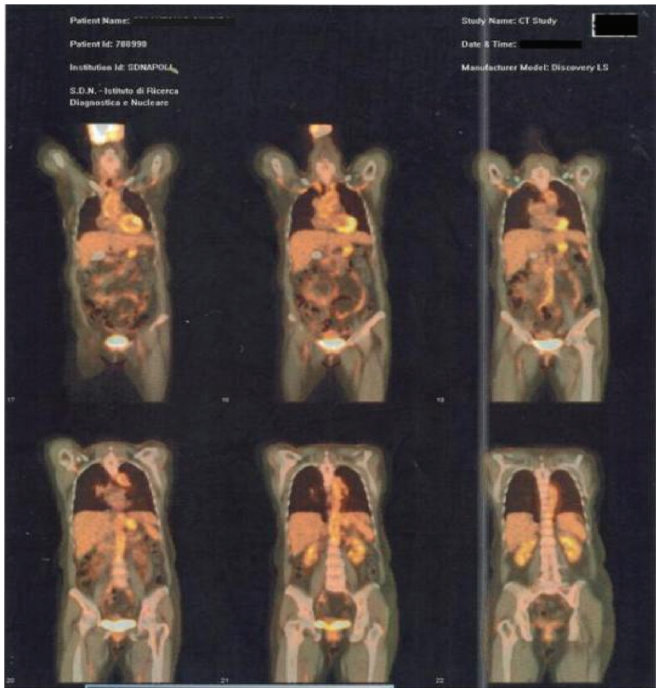

Fig. 1.

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SJÖGREN'S SYNDROME BEGINNING AS A CASE HISTORY OF MYOSITIS: A CASE REPORT

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We report the case of a 74-yr-old woman with progressive muscle weakness that lasted 8 months. Laboratory data revealed a Creatine kinase (CK) concentration wery high (1008 U/l). Thyroid hormones were normal. Since 2 months the patient reported slight dyspnoea and dry cough, with sicca syndrome. At the time of admittance in hospital Schirmer's test was positive, and she was positive for ANA 320 (nucleolar pattern) and SSB/La+. A minor salivary gland biopsy revealed diffuse lymphocytic infiltrates around the ducts, with a focus score of 1.1/mm2 according to Chisholm's classification. Chest X-ray and capillaroscopy were negative. After 1 week of steroid therapy (prednisone 0.5 mg/kg) CK decreases to 54 U/l, and muscle weakness improved and consequently we delayed to perform a muscle biopsy. We discharge the patient with diagnosis of Sjogren's syndrome with Xerotrachea, and started therapy with Methotrexate 10 mg/w/im, metilprednisolone 8 mg/die and bromhexine syrup. After 2 months, the patient referred absence of muscle weakness and cough, amelioration of sicca syndrome.
Our case presents several peculiarities: The muscle weakness with elevated CK started off six months before sicca syndrome, mimicking a primary myositis. An inflammatory muscle disease is associated with 4-16% of systemic lupus erythematosus patients, while rheumatoid arthritis occurs in 3-5%, but myositis is found only in 3% of SS patients. Moreover, in literature, the cases of myositis associated with SS present higher prevalence of SSA/Ro positivity, whereas our patient had SSB/La positivity, and incontrovertible diagnosis of SS was done only with labial gland biopsy.

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A PAEDIATRIC CASE OF LIPOATROPHIC CONNECTIVE TISSUE PANNICULITIS

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Lipoatrophic panniculitis is a rare disease, only exceptionally described in children. A thirteen years old girl presented with a four months history of recurrent crops of painful, tender subcutaneous nodules of the limbs and migrant lower legs arthralgias. Skin examination disclosed several annular lesions with erythematous indurated borders and slight cup-shaped subcutaneous central atrophy, in the forearms, in the internal of thighs and in the dorsal legs and feet (Fig 1).

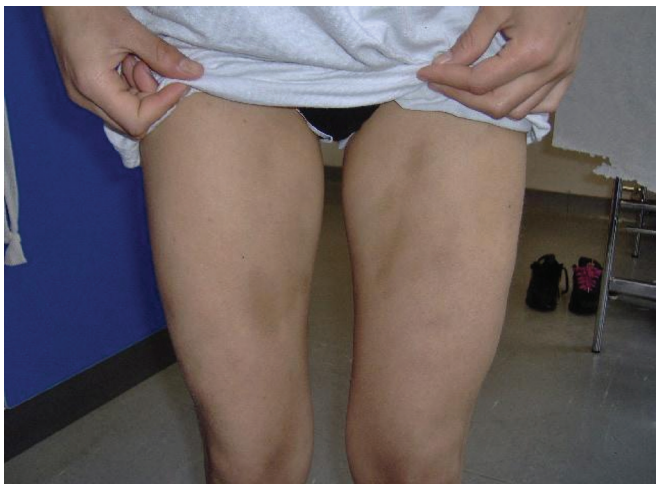

Fig. 1

The lesions had recurred in crops over the previous months resulting in severe asymmetrical lipoatrophy of the limbs. The patient was started on daily prednisone which gradually led to improvement of her symptoms and signs, steroid was tapered over 1 month. Two weeks after steroid suspension, the patient showed an exacerbation with new lesions in the thighs and in the arms. She was started daily steroids again to suppress the acute exacerbation. Once it has been suppressed, she was started on daily hydroxychloroquine.
Our patient presents a severe, chronic, atrophic lobular panniculitis, without vasculitis; no systemic involvement is present, except for arthralgia at the beginning. Effective therapy options for patients with lipoatrophic connective tissue panniculitis are limited, the disease evolution tends to be chronic and esthetic sequelae are severe.

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AUTOANTIBODIES AND CLINICAL FEATURES CAN PREDICT EVOLUTION IN PATIENTS WITH MCTD

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Objective: To define predictors (autoantibodies and clinical features) of evolution towards other connective tissue diseases (CTDs) in patients with the initial diagnosis of mixed connective tissue disease (MCTD) and to find out associations between autoantibodies at disease onset and development of a specific organ involvement during the course of the disease.
Methods: Clinical and serological features of 161 patients with the initial diagnosis of MCTD were evaluated retrospectively at the diagnosis and in 2008, after a mean disease duration of 7.9 years. Patients who satisfied at diagnosis either classification criteria for Kasukawa, Alarcón or Sharp have been evaluated separately and reclassified in 2008 according to their evolution. Statistical analysis were performed

to find out predictors of evolution into other CTDS and of development of a specific organ involvement.
Results: Anti-dsDNA turned out to be associated with evolution into systemic lupus erythematosus (SLE) both in patients with a first diagnosis of MCTD according to Kasukawa (p=0.012) and Alarcón-Segovia criteria (p=0.001). Sclerodactyly (p=0.034) and esophageal hypomotility or dilatation (p<0.001) were independently associated with evolution into systemic sclerosis (SSc) in patients satisfying Kasukawa criteria at disease onset. The presence of the following autoantibodies at MCTD diagnosis was associated with specific organ involvement in 2008: anti-Sm with renal involvement (p=0.004), anti-SSA/ro with neurological involvement (p=0.014), anti-Scl70 with esophageal hypomotility (p=0.048).
Conclusions: A careful analysis of clinical and serological features at MCTD onset can help the physician in predicting disease evolution. Autoantibodies may be considered as a warning for the development of severe complications.

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ULTRASOUND LUNG COMETS (ULC) MAY HELP THE SCREENING OF INTERSTITIAL LUNG DISEASE (ILD) IN SYSTEMIC SCLEROSIS (SSC)

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Background: Chest high resolution computer tomography (HRCT) is used as routine evaluation of interstitial lung disease (ILD) in systemic sclerosis (SSc). Ultrasound lung comets (ULC, also called B-lines) evaluated by lung ultrasound are an echographic sign of alveolar-interstitial syndrome. Recently, ULC have been suggested as a sign of ILD in SSc, due to significant correlation with a HRCT score of pulmonary fibrosis.
Objective: To evaluate the correlation between HRCT and ULC in the diagnosis of ILD in SSc.
Methods: Twenty-three patients (females=22, mean age 53.5±15.6) with a diagnosis of SSc underwent lung ultrasound and chest HRCT. We evaluated location and number of ULC on both hemithoraxes, at specific predefined scanning sites. Then we compared the data with fibrosis areas disclosed at HRCT, using Phi correlation agreement for dichotomous categorical variables.
Results: In 22 patients (96%) we observed a good correspondence between ULC and HRCT results (Phi=0.67, p=0.001). In 1 patient (4%) lung ultrasound data did not correspond to HRCT evidence of ILD because the limited area of fibrosis (3 mm) detected at HRCT was not detected at lung ultrasound. In 12 patients (52%) ULC was the first indicator of ILD, later confirmed with HRCT.
Conclusions: These data confirm that ULC may detect ILD in SSc and are significantly correlated with HRCT. The advantages of ULC are the low cost, the feasibility and the safety (non x-ray exposure). In the future, ULC may become a screening technique useful for the early detection of ILD in patients with SSc.

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IN VITRO AND *EX VIVO* EFFECTS OF ANTI-B_2GLYCOPROTEIN I ANTIBODIES ON PLATELET AND ENDOTHELIAL ACTIVATION

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Aims: We evaluated the effects of anti-β_2 GPI antibodies ($a\beta_2$GPI) on platelet and endothelial activation in women with antiphospholipid syndrome (APS).
Methods: For *in vitro* studies $a\beta_2$GPI were isolated from the plasma of a pregnant woman with APS during two different stages (catastrophic and quiescent). Platelet surface P-selectin (P-sel) expression as a marker of platelet activation was assessed by flow cytometry. Plasma samples from patients with catastrophic APS (n=4), with quiescent APS (n=6) and from healthy controls (n=5) were collected for *ex vivo* studies. Some markers of platelet activation such as sP-sel and sCD40L (by ELISA), MMPs (by zymography), and of endothelial activation: sVCAM and MCP-1 (by ELISA) were also measured.
Results: According to *in vitro* results $a\beta_2$GPI can induce platelet activation only in the presence of a platelet agonist (TRAP-6) at a subthreshold concentration. Notably, $a\beta_2$GPI enhanced the platelet surface P-sel expression more in the catastrophic than in the quiescent phase of the same patient (47% versus 15%). The *ex vivo* studies demonstrated that APS patients had higher levels of platelet and endothelial activation markers in comparison with control subjects. The titres of these markers were even higher in catastrophic than in the quiescent APS.
Conclusions: Our study showed $a\beta_2$GPI can enhance the platelet activation and is more active in catastrophic APS. There is moreover an high numbers of platelet and endothelial activation markers in APS patients and especially in those during a catastrophic stage.

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ANTIPHOSPHOLIPID ANTIBODY ISOTYPES AND TARGET AUTOANTIGEN SUBGROUPS AS PREDICTORS FOR DIFFERENT CLINICAL MANIFESTATIONS OF ANTIPHOSPHOLIPID SYNDROME

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Aim: To investigate the isotypes of antiphospholipid antibodies (APLA) in patients with different clinical manifestations of antiphospholipid syndrome (APS).
Patients and methods: 568 patients who had tested positive for APLA (Anti-Phospholipid Screen IgG/IgM, Orgentec, Germany) were evaluated retrospectively. Anticardiolipin (ACL), anti-beta-2-glycoprotein-1 (AB2GP1), anti-phosphatidylserin (APSe), anti-phosphatidylinositol (API) and anti-phosphatidic acid (APA) IgG and IgM antibodies were determined by ELISA (ThromboCombo, Orgentec).
Results: Over the years, only 61 individuals (11%) have shown repeated APLA positivity and have fulfilled APS classification criteria. In 46 female and 15 male patients with a mean age of 43±12, 13/61 individuals have suffered from recurrent miscarriages, 35/61 patients have shown symptoms of peripheral vein thrombosis and 13/61 patients have shown symptoms of arterial thrombosis in different locations. In women with recurrent miscarriages, APLA IgM were more common than APLA IgG and than APLA IgM/IgG double-positive findings (p=0.012 and p<0.001, respectively). In other APS cohorts, distribution of APLA isotypes was equal. In APS patients with miscarriages, concentrations of all APLA examined were significantly lower than in other groups. In *logistic regression* analysis, combination of AB2GP1+ACL and AB2GP1+APSe showed the highest association with miscarriages (*odds* ratio [OR]=2.29, p<0.032 and OR=1.96, p=0.042, respectively). Combinations of AB2GP1+ACL+APSe and AB2GP1+ACL+APA showed significant associations with venous thrombosis (OR 2.16, p=0.029 and OR=2.24, p=0.025, respectively).
Conclusions: The combination of distinct antiphospholipid antibody isotypes and target autoantigen subgroups seems to predict different clinical manifestations of APS.
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SUCCESSFULLY DELIVERED A PATIENT WITH SECONDARY APS DUE TO SLE

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A 33-year-old woman admitted to our rheumatology clinic for secondary APS due to SLE. She had been diagnosed as SLE in 1998. In 2006, a stillbirth had been observed at 38th week. In 2004, she had developed an abortion at 7th week of her pregnancy. She had been used to prednisolone, aspirine, and hydroxychloroquine for SLE. Hereby, she was on remission, and had a pregnancy at 10th week. She was using to low dose aspirine (LDA) for a long time. Due to pregnancy, and pregnancy losses, despite thrombocytopenia, we started low molecular weight heparine (LMWH); anti-Xa (enoxaparine sodium) 4000 IU/ml/day, and prednisolone 20 mg/day. ACAs, APAs, and Anti-SS-A(Ro-52/60 kD) were positive. C3 level was low. LDA, LMWH, prednisolone, calcium, and vitamin D3 were administered. But, she had severe thrombocytopenia (20.000c/L). Therefore, 400 mg/kg/monthly IVIG was started, and maintained during pregnancy. LMWH using was maintained until six hours to C/S. A healthy baby was born. After delivery, LMWH was used for eight weeks. On her follow-up, no arterial or venous thromboses were observed.
The management of the APS during pregnancy is difficult, controversial. LDA, LMWH, steroid, IVIG, azathioprine could be used, but rituximab is controversial on pregnancy. Even if that infants are asymptomatic should be cautiously monitored. Especially, mothers with positive autoantibodies (e.g., anti-Ro and La), infants might be develop cardiac, dermatologic, haematologic, hepatic manifestations. Using IVIG plus steroid during pregnancy in patients with APS can be beneficial in reducing early myocardial inflammation, and future fibrosis.

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PRIMARY ANTIPHOSPHOLIPID SYNDROME (PAPS) AND THE EVOLUTION TO LUPUS: ANY ROLE FOR THE HLA SYSTEM AND THE ANTI NUCLEAR FACTOR?

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11 patients (aged 16-48 years) who had never manifested features of SLE at the time of diagnosis of PAPS were followed up. After an average period of 6.8 years, 3 (23%) progressed into clinico-immunological SLE. Three (27%) expressed positive anti-ds DNA antibodies and/or anti-Sm antibodies, periodically or constantly, without manifesting clinical lupus. In order to understand such phenomenon, we focused on class I and II major histocompatibility system (MHC) and anti-nuclear factor (ANF) profiles. Only nine underwent tissue typing.
The HLA-A2 was exclusively present in those evolved into clinical or serological lupus 5/6. The HLA-B profile was diverse and non-contributory. In class II MHC, there was a clustering of DR4, pointing towards disease association as compared to controls, 6/9 (66.5%) vs. 153/ 604 (25.5%), RR=5.71, 95% CI=1.44-22.56 & p=0.01). The antigen was distributed throughout the 3 subgroups. Prevalence of DQ 3 (6/9, p=NS) was frequent but nondiscriminatory. No specific haplotype was found to be associated with these patients.
All six patients showed a marked rise in the ANF titre from an average of 1:160 during the diagnosis of PAPS to a strongly positive titre of an average of 1:1253, p=0.03 around or beyond the time of evolution.
Conclusions: There was no clue from the HLA typing towards the evolution in to lupus apart from clustering of A2 in evolved cases. Data of ANF makes the periodic assay of the factor highly imperative as its upsurge could herald the event of evolution.

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THE INTIMA MEDIA THICKNESS MEASUREMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS AS A MIGHTY TOOL IN ATHEROSCLEROSIS ASSESSMENT REGARDING SECONDARY ANTIPHOSPHOLIPID SYNDROME

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Objectives: Patients with Systemic Lupus Erythematosus (SLE) have an increased risk of atherosclerosis. The aim of our study was to evaluate importance of antiphospholipid syndrome (APS) presence in changes of carotid intima media thickness (IMT) in SLE patients.
Methods: Our study included 120 patients with SLE (45.67±12.14years), 108 women and 12 men. Among them, 58 patients had secondary antiphospholipid syndrome (sAPS) and 62 patients were with no presence of sAPS. The two groups were comparable with respect to age, gender, disease activity (SLEDAI), manifestations of the main disease, and there was no difference considering traditional risk factors. All patients underwent assessment of carotid IMT by Doppler ultrasonography. The findings were significant if IMT was greater than 1.1 mm. In order to determine APS significance in older age, patients were classified in three age groups (<35 years, 35 to 55 years and >55 years).
Results: 49.4% pts with sAPS had significant changes of carotid arteries comparing to 16.8% pts without APS (p=0.007). Multivariate regression analysis revealed APS as a significant predictor of plaque presence (p=0.025) with almost same strength as hypertension (p=0.031). Considering age, in group >55 years, APS was significantly related to plaque presence since 90.89% of patient with carotid artery changes had APS (p=0.041).
Conclusion: Presence of APS in SLE patients is a predictor of significant carotid arteries IMT changes. Early carotid atherosclerosis in patients with secondary APS is probably a result of cumulative immune activity. The importance of secondary APS presence in SLE patients is significant in older patients, too.

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LEVELS OF ANTIPHOSPHOLIPID ANTIBODIES AND SKIN LESSIONS IN ANTIPHOSPHOLIPID SYNDROME PATIENTS: DOES ASSOCIATION EXIST?

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Introduction: Antiphospholipid syndrome (APS) patients express skin manifestations with the presence of various levels of antiphospholipid antibodies (aPL).
Objectives: Aim of this study was to investigate association between aPL type and level and skin manifestations in APS.
Patients and methods: Our prospective study comprises 256 patients: 162 primary APS patients (94 female and 68 male, mean age 45.2±12.9 years) and 94 Systemic Lupus Erythematosus (SLE) patients with secondary APS (83 female and 11 male, mean age 43.1±15.4 years); aPL analysis included: LA and aCL (IgG/IgM), β_2GPI (IgG/IgM), by positive titers: low (10-30), medium (30-100), and high (>100PLU/ml). In all patients, we collected data considering frequently occured skin lesions.
Results: Our results performed on total APS patiens and both PAPS and SLE groups didn't show correlation between skin lesions and aPL type and level.
The exeptional results in APS patients showed that skin ulcerations correlated with both high levels of aCL IgM and β_2GPI IgM (p=0.013 and 0.044) while pseudovasculitis correlated with high levels of β_2GPI IgM (p=0.017) .
In SLE group, livedo reticularis and pseudovasculitis correlated with high levels of β_2GPI IgM (p=0.008 and 0.032) and skin ulcerations with high levels of aCL IgM (p=0.049).
Conclusion: Our results showed correlation between skin lesions and levels of aPL. High levels of β_2GPI IgM might predict skin ulcerations and pseudovasculitis in APS patients. Pseudovasculitis commonly occured with high levels of aCL IgM. High levels of β_2GPI IgM are more common with livedo reticularis in SLE patients.

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POSSIBLE ASSOCIATION BETWEEN RHEUMATIC HEART DISEASE AND SYSTEMIC LUPUS ERYTHEMATOSUS WITH ANTI PHOSPHOLIPID SYNDROME

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Rheumatic heart disease (RHD) is the result of cardiac involvement by rheumatic fever (RF). Endocardial involvement is an essential component of such affection that can end by multivalvular dysfunction and disability. Antiphospholipid syndrome (APS) is a condition characterized by a constellation of manifestations; most common of these are recurrent deep vein thrombosis, fetal losses, thrombocytopenia, neurological features, livedo reticularis, hemolytic anemia, cardiac affection and auto antibodies known by anti-phospholipid antibodies.
Although the two conditions have different clinical pictures, yet there are several common characteristics that link the two diseases.
The association of RHD and SLE with secondary APS was not previously reported in the literature. We are investigating whether the presence of valvular heart pathology secondary to rheumatic fever (RF) increases the risk for the development of autoimmune diseases with APS.
Considering the high prevalence of RHD in Egypt we sought to analyze the possible inter-association between RHD and autoimmune disease affecting the heart especially in SLE patients with APS.
In conclusion, there may be a possible increased susceptibly in patients with cardiac pathology due to RHD to acquire another autoimmune illness affecting the heart such as APS with or without SLE.

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AN UNUSUAL CASE OF CORONAROPATHY

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The relationship between viral infections and induction of anti-phospholipid antibodies is well known, but case reports of related thrombotic events are rare in literature, especially those involving the coronary circle.
We report a case of Dengue hemorrhagic fever complicated by developing of anti-phospholipid antibodies (aPL) and related coronaropathy.

A 45-year-old man experienced a myocardial infarction in absence of conventional cardiovascular risk and without a familiar history of ischaemic heart disease.
Coronarography showed subcritical stenosis in the anterior interventricular artery and tight thrombus in the right coronary artery with no evidence of atherosclerotic disease. Coronary angioplasty was performed successfully.
Coagulation screening for hereditary thrombophilia was negative.
Autoantibody screening showed positivity for IgM aPL and lupus anticoagulant antibodies (LAC); no other autoantibodies were detected. The positivity of aPL and LAC was confirmed 12 weeks later.
Of note, this patient had spent a period in Brasil some months before and was hospitalized for Dengue hemorrhagic fever there.
Dengue is an infectious disease caused by a virus of the Flavivirus genus which is transmitted by arthropods.
Anti-phospholipid antibodies and lupus anticoagulant are associated with a number of viral infections, including Flavivirus.
The clinical significance of aPL antibodies in patients with viral infections remains unknown. In some patients, these antibodies may be transient and disappear within 2 or 3 months. In other susceptible individuals, they may persist and cause clinical events.
We hypothesize Antiphospholipid Syndrome (APS) secondary to Dengue virus infection as the responsible for myocardial infarction in this specific case.

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PREGNANCY OUTCOME IN "INCOMPLETE" OBSTETRIC ANTIPHOSPHOLIPID SYNDROME: A RETROSPECTIVE STUDY OF 156 PREGNANCIES

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Introduction: There is no consensus concerning treatment of "incomplete" Obstetric Antiphospholipid Syndrome (OAPS).
Objectives: To evaluate Low Dose Aspirin (LDA) efficacy by comparison of pregnancy outcome in treated and untreated women with "incomplete" OAPS and to compare antiphospholipid antibody (aPL) profile with pregnancy outcome in all these patients.
Methods: 156 pregnancies of 133 women (mean age 34.2 years ± 4.2 SD; range 22.8-44.4) with "incomplete" OAPS, 120 treated with LDA and 36 untreated, were studied retrospectively between 1993 and 2010. Inclusion criteria were: a) one or two abortions and complete laboratory criteria, b) complete obstetric criteria and low-titre aPL positivity, c) no obstetric history but complete laboratory criteria. Anticardiolipin (aCL) and anti-beta 2-glycoprotein I antibodies were measured using home-made ELISA assays and Lupus Anticoagulants (LA) were analyzed following internationally recognized guidelines. Chi-square and Fisher's exact tests were used to analyze the data.
Results: There were 141 live births (90.4%) with a mean gestational age of 38.4 weeks ± 2.1 SD (range 27-42) and a mean weight of 3212.6 g ± 603.2 SD (range 700-4650). Spontaneous pregnancy losses, all occurring between the 6^{th} and 21^{st} weeks of gestation (mean 10.1 ± 4.1 SD), were registered in 15 cases (9.6%). Pregnancy outcome in the LDA-treated patients was not significantly different from that in untreated women. Spontaneous pregnancy loss was significantly higher in patients with medium-high levels of IgG aCL (p=0.02). LA positivity was significantly associated with premature births (p=0.038).
Conclusion: Randomized controlled trials are warranted to verify these results.

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ANTI-LIVER AND ANTOENDOMYSIAL AUTOANTIBODIES IN PRIMARY ANTIPHOSPHOLIPID SYNDROME

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Background: Autoimmune liver disease (ALD) may be associated with other autoimmune disorders in 20-40% of patients. Only few cases of ALD and antiphospholipid syndrome (APS) were described but we could not find any study about frequency of anti-liver autoantibodies in APS.
Objective: The aim of this study was to evaluate the prevalence and clinical significance of circulating anti-liver and anti-endomysial autoantibodies in patients with primary antiphospholipid syndrome (PAPS).
Methods: Clinical and serological data from 40 PAPS patients (7M/38F), aged from 20 to 66 years were analyzed. All patients fulfilled the Sapporo criteria for APS. Exclusion criterion was the presence of other autoimmune diseases. Sera samples were tested for anti-liver antibodies: anti-smooth muscle (ASMA), anti-liver-kidney microsome type 1 (ALKM-1), anti-parietal cells (APC), anti-mitochondrial (AMA) and anti-liver cytosolic protein type 1 (ALC-1), and anti-endomysial (AEM) antibodies using standard techniques.
Results: The mean age of the participants was 41.6 ± 11.2 years, 84.4% female and 77.7% white. The mean disease duration was 85.18±68.2 months. Arterial thrombosis was observed in 42.2%, venous in 53.3%, abortion in 22.2%, livedo reticularis in 31.1% and thrombocytopenia in 13.3%. Lupus anticoagulant was present in 62.2% and IgG/IgM anticardiolipin in 44.4%. Anti-liver antibodies positivity were observed in 3 (6.7%). Specifically, ASMA antibodies were detected in 0 patients, AMA in 1 (2.2%), ALKM-1 in 1 (2.2%), APCA in 2 (4.4%), ALC-1 in 0, and AEM in 0.
Conclusion: Positivity for antibodies against liver antigens and against endomysial, by highly specific techniques, was rarely observed in PAPS patients.

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DIFFERENT ANTIPHOSPHOLIPID ANTIBODIES IN SLE PATIENTS

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Background: The diagnostic significance of different antiphospholipid antibodies (cardiolipin-ACL, beta-2-glycoprotein I-B2GPI, phosphatidylserine-PS, annexin V-AnV, prothrombin-PrT, phosphatidylethanolamine-PE) in SLE patients with and without clinical data for antiphospholipid syndrome (APS) has been studied by many authors but remains controversial. The clinical importance of these antibodies is unclear.
Aim: To investigate the levels of IgG and IgM of different antiphospholipid antibodies in patients with SLE with and without APS.
Patients and methods: We investigated the serum levels of IgG and IgM antibodies in 30 patients with SLE (26 female, 4 male, aged 10-78 years, 19 with and 11 without APS) and in 38 healthy volunteers (19 female, 19 male, aged 17-45 years), using ELISA method. The main clinical manifestations for APS were pulmonary embolism, spontaneous abortions, deep venous thrombosis,myocardial infarction, stroke.
Results: High levels of IgG and/or IgM ACL and/or B2GPI were found in all of SLE patients with APS and only in 2/11 with SLE patients without APS. On the other hand, part of the patients without data for APS had antibodies to other phospholipids.
Conclusions: The diagnostic significance of different antiphospholipid antibodies in SLE patients without clinical data for APS remains unclear, but maybe the high values of antibodies to PS, AnV, PrT and PE also support the diagnosis APS. The investigation of these antibodies should be a part of the screening panel.

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PREGNANCY OUTCOMES IN A COHORT OF AUTOIMMUNE PATIENTS

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The impact of maternal autoimmune diseases on pregnancy outcome is not unequivocally defined [1-2-3].
We analyze pregnancy outcome of 262 pregnancies from 219 autoimmune patients, consecutively followed in a single Italian reference center from 2001 to 2009. All patients were prospectively followed with monthly visits. Pregnancy outcome was compared with the previous obstetrical history. Women were divided into 5 groups: primary APAS(APAS-I, 39 patients), secondary APAS(APAS-II, 17 patients), rheumatic diseases(RD, 92 patients), isolated autoAbs(anti-nuclear or anti-phospholipid, 79 patients) and either Rheumatoid Arthritis or Spondyloartropathies(AR-S, 35 patients). The 48.9% of patients had anamnestic pregnancy complications. In the pregnancies followed in our Clinic, complications dropped to 28.7%. Mean neonatal weight was 3051±569g; mean gestational age at delivery 38.38±2.34 weeks. 9% had preterm delivery and 11.1% newborns had low weight at delivery. APAS-II patients had the worst outcomes: 27.3% miscarriage, 12.5% growth restriction and 25% preterm delivery. In contrast, pregnancies in patients with APAS-I, RD or AR-S had satisfactory outcomes. Despite the high frequency of anamnestic adverse events (44.7%), pregnancies from isolated autoAbs patients had a satisfactory outcome.
Our experience suggests that a strict follow-up/targeted treatments improve pregnancy outcomes in autoimmune patients, including those with isolated autoAbs and a poor anamnesis. Patients with APAS-II fail to respond. Further studies are necessary to understand the molecular events underlying this heterogeneity.

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ANTIPHOSPHOLIPID ANTIBODY MAY DOWN-REGULATE ENDOTH THROMBOMODULIN, A MECHANISM FOR HYPER-COAGULATION

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Antiphospholipid syndrome (APS) was characterized by hypercoagulation with clinical manifestation of arterial or venous thrombosis. Variants of antiphospholipid antibody were found to induce hypercoagulation after targeting to different antigens. In this study, human umbilical cord vein cells (HUVECs) were incubated with IgGs isolated from 12 patients with APS and 3 aCL hybridoma monoclonal antibodies for 6 hours. Expression of thrombomodulin (TM), tissue factor (TF) and ATP diphosphohydrolase were analyzed on cell surface by flow cytometry. Level of soluble TM, soluble tissue factor, von Willebrand factor (vWF) were measured in cultural supernatants by ELISA. We found IgG from patients and IS6 aCL hybridoma monoclonal antibody resulted in a significant decrease of TM on HUVECs. IgG from 3 patients and IS4 monoclonal antibody resulted in a significant increase of TF on HUVECs. vWF level increased after incubation with IgG from 4 patients and all 3 hybridoma monoclonal antibodies. On the contrary, soluble TM decreased after antibody treatment.
In conclusion, these finding suggest that IgG from APS patients and hybridoma monoclonal antibodies may create a hypercoagulable state after interacting with endothelial cells by the decrease of anti-coagulant and the increase of pro-coagulant molecules on the endothelial cells.

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MANAGEMENT OF SARCOIDOSIS: DON'T FORGET THE HEART!

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Introduction: Sarcoidosis is a systemic disorder of uncertain etiology characterized by noncaseating granuloma and increased cellular immune response at sites of disease activity. Involvement of the heart by sarcoidosis has been reported in 20-70% of patients in autopsy series but only 5% or less develop clinical evidence of cardiac impairment. The antemortem diagnosis of cardiac sarcoidosis is frequently missed because the disease can mime many common clinical entities. Cardiac involvement usually includes granulomatous inflammation or fibrosis of the myocardium, conduction system, or pericardium. Vascular involvement of epicardial coronaries is limited to recent isolated case reports.
Case report: We describe a case of a 38-years-old white woman with a known history of pulmonary sarcoidosis on steroid therapy since two years, presented with severe chest pain and evidence by electrocardiogram of acute anterior ST-elevation myocardial infarction. Coronary angiography showed extensive stenosis of the left anterior descending coronary-artery, followed by a wide coronary-artery dissection. Therapy with heparin and aspirin, as well as beta-blockers and statins, was initiated, and percutaneous coronary intervention with stenting of the entire length of the dissection was performed.
Conclusions: This first report of spontaneous coronary-artery dissection in patient with sarcoidosis highlights the need for an accurate cardiovascular work-up in patients affected. A high index of suspicion for a non atherosclerotic cause of inflammation and an early recognition of unusual cardiovascular manifestations can play a decisive role in the management of the disease as well as in the improvement of the prognosis.

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MULTIPLE CRANIAL NEUROPATHIES, A RARE COMPLICATION OF SYSTEMIC SCLEROSIS

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Introduction: Systemic sclerosis can rarely have neurological manifestations. We present what we believe is the first case of a patient with opthalmoplegia due to systemic sclerosis.
Case report: A 45 year old woman with a 5-year history of anti-Scl-70 positive systemic sclerosis was admitted for elective amputation of a long standing necrotic digit. During her stay she developed multiple cranial nerve palsies including right third and sixth nerve palsies and a left twelfth nerve palsy. After thorough investigation, no evidence of active infection, malignancy, thrombosis or neuronal inflammation could be found. Consequently, an acute-phase response with a background of connective tissue disease suggested vasculitis as a cause of the cranial neuropathy. The patient responded promptly to methylprednisolone. Subsequent treatment of cyclophosphomide led to complete resolution of symptoms.
Conclusion: Neurological involvement in systemic sclerosis, which includes stroke, depression and peripheral nerve dysfunction, is uncommon and usually attributed to the micro-angiopathy associated with the disease. Cranial neuropathies in systemic sclerosis are very rare. When reported, the onset is usually insidious. Most often the trigeminal nerve is affected but other affected nerves include: facial nerve, chorda tympani, vestibulochochlear nerve, glossopharyngeal nerve and hypoglossal nerve. To the best of our knowledge, this is the only case of occulomotor and abducent nerve palsy in systemic sclerosis that has ever been reported. Vasculitis is a genuine complication of systemic sclerosis and should be considered early in such presentations. Robust and rapid immune-suppression can mitigate the course of the disease and minimise damage.

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THE ROLE OF MAGNETIC RESONANCE IMAGING IN THE ASSESSMENT OF IDIOPATHIC INFLAMMATORY MYOPATHIES

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Objectives: Magnetic Resonance Imaging (MRI) can detect inflammatory muscle edema in active myositis but few studies have correlated MRI with clinical and laboratory data. The aim of this study was to evaluate the potential relationship between MRI edema of thigh muscles, the increase in muscle enzymes and muscle weakness in patients with Idiopathic Inflammatory Myopathies (IIM).
Methods: We enrolled in two Rheumatology centers 39 patients, 17 Dermatomyositis, 14 Polymyositis, 2 paraneoplastic Dermatomyositis, 4 Anti-synthetase syndrome, 2 Overlap Syndromes and 1 Inclusion Body Myositis. Myositis was diagnosed according to the Bohan and Peter criteria, muscle histology findings, and autoantibodies. In all patients, creatinephosphokinase (CK) was measured and muscle strength evaluated by manual muscle test (MMT). MMT was assessed in 12 muscle groups and graded using the 0-5 Medical Research Council scale. T1/T2-weighted and STIR MRI sequences were acquired at the same time of MMT. The presence of edema as high-signal areas within each of the seventeen thigh muscles was assessed (1=present, 0=absent) to generate a score ranging from 0 to 17.
Results: Multivariate analysis showed a significant correlation between MRI and MMT of the thighs (r: 0.33; $p<0.04$), while no significant correlation between MRI and CK or between MRI and global MMT was found.
Conclusions: Our data, although preliminary, suggest in agreement with literature that MRI is a useful method to assess muscle involvement in patients affected by IMM. Our future plan is the evaluation of patients with non-inflammatory myopathies to define the specificity of MRI.

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INFLUENCE OF DELAYED DIAGNOSIS ON THE COURSE OF CHURG-STRAUSS SYNDROME

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Introduction: Churg-Strauss syndrome (CSS) is a rare, systemic, necrotizing, small vessel vasculitis with blood eosinophilia, eosinophil tissue infiltration and asthma. The disease is not rarely diagnosed with delay.
Aim of the study: To evaluate the influence of delayed diagnosis and treatment on the course of CSS.
Patients and methods: Hospital charts of 23 patients (15 women, 8 men) with CSS treated in the Jagiellonian University Hospital (Cracow, Poland) between years 1999-2010 were retrospectively analyzed. Detailed patients history was taken and additional investigations (imaging and laboratory data) were analyzed. The CSS diagnosis was reassessed and confirmed with the current American College of Rheumatology (ACR) guidelines. The delay between the time when ACR criteria for CSS were met and the proper diagnosis was calculated, and patients were divided into two groups: group I (10 patients) with a delay of more than 1-month (7.20±3.01); group II (13 patients) with a shorter delay (0.31±0.23).

Results: Table I.

Clinical course of CSS	Group I (n=10)	Group II (=13)	*p*
EF LV (%)	60.10±15.70	55.92+16.41	NS
skin lesions	90%	38.46%	*p*=0,029
presence of ANCA	0%	38.46%	*p*=0,046
frequency of CSS exacerbations requiring hospitalization (per years)	2.30±1.03	0.61±0.39	<0,0001
Treatment during remission:			
doses of oral glucocorticosteroids - as methylprednisolone (mg/day)	11.40±4.72	5.85±2.07	*p*=0,039
additional immunosuppression	90%	53.85%	NS

NS: no statistical significance; EF LV: ejection fraction of the left ventricle; ANCA: anti-neutrophil cytoplasmic antibodies.

No statistically significant differences in the presence of dysfunctions of the cardiovascular system, peripheral and central nervous system, urinary tract and gastrointestinal tract were observed.
Conclusions: The delay of the diagnosis seems to have a negative impact on the course and treatment of CSS. Lack of ANCA seems to influence the protraction of the diagnosis process.

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AUTOIMMUNITY AND BRAIN - MORE TO IT THAN JUST PSYCHIATRICS

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Neuropsychiatric symptoms are relatively frequent in patients with autoimmune diseases, occurring either prior to the diagnosis or during the course of their illness. These manifestations may mimic symptoms due to intercurrent illness, medication use, and functional disturbances of the disease.
The frequency of neuropsychiatric symptoms appears to be increasing because of both better testing and increased physician awareness.
In this review we determined the prevalence of neuropsychiatric symptoms in individuals with autoimmune diseases and described the morbidity and burden in quality of life for these subjects.
We analyzed the symptoms of 136 patients followed between January 2008 and October 2010, in an outpatient clinic of Autoimmune Diseases. The median age was 40, 2 years old, with a female preponderance. Thirty-nine patients had systemic lupus erythematosus, twenty-seven patients had antiphospholipid syndrome, twenty-eight patients with Behçet´s disease, eleven patients with scleroderma, among others.
In these patients, 39% had neuropsychiatric symptoms. All of these patients were medicated. The majority of them with sedatives and/or antidepressants. Initial symptoms, problems in diagnosis and differential diagnosis, treatment adopted and evolution of the disturbances are described.
To better understand the mechanism of this disturbance in autoimmune diseases, it is imperative to be aware of this problem. Improving tests and searching for molecular markers may help physicians, not only in the treatment but in preventing this burden in patient's quality of life.

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ANTI-TNF BLOCKAGE MAY IMPROVE OCULAR SURFACE PARAMETERS OF PATIENTS WITH RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS

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Objective: To compare clinical and functional ocular surface parameters of patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) before and after anti-TNF treatment.
Methods: Twenty-nine patients with RA (n=15) and AS (n=14) were examined for dry eye. They were evaluated at baseline (BL), 3 (3M) and 12 months (12M) after anti-TNF treatment. The patients answered the Ocular Surface Disease Index (OSDI) questionnaire and underwent Schirmer's test, tear breakup time test (BUT), fluorescein and lissamine green staining as well as lesion grade of bulbar conjunctival cells by impression cytology.
Results: Mean age of patients was 47.4±12.9 years, 59% were female gender and 93% Caucasian race. Mean disease duration was 19.9±9.4 and 17.8±11.8 years in RA and AS patients, respectively. Infliximab was used in 40%, etanercept in 47% and adalimumab in 13%. Interestingly, there was an increase in Schirmer's test values comparing BL with 3M evaluation in RA patients (16.9±12.5 mm vs. 21.6±12.8 mm, p=0.01) while 12M: 20.5±11.7 mm values were comparable to BL evaluation. No differences were observed in these parameter for AS patients (BL: 15.0±10.5mm, 3M: 18.3±11.1mm, and 12M: 18.5±10.1 mm). Remarkably, a significant improvement of the cytological lesion grade was achieved at 12M evaluation in AS patients (BL: 78.6% vs. 12M: 35.7%, p=0.031). BUT, fluorescein, lissamine green staining and OSDI scores were similar before and after treatment for RA and AS patients.
Conclusion: Anti-TNF therapy may promote recovery of tear production in AR patients and improve conjunctival cytological lesion grade in AS subjects.

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SUMO4 C438T POLYMORPHISM IS ASSOCIATED WITH PAPULOPUSTULAR SKIN LESION IN KOREAN PATIENTS WITH BEHÇET'S DISEASE

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Objects: Small ubiquitin-like modifier 4 (SUMO4) is involved in a range of autoimmune diseases and is known to down-regulate the transcription activity of nuclear factor kappa B (NF-kB). Our objective was to investigate the association of a certain polymorphism (C438T) of the SUMO4 gene with Behçet's disease (BD) in terms of its incidence and clinical features in Korean patients.
Methods: We consecutively enrolled 83 patients with BD and 120 healthy controls. Genomic DNA was extracted from whole blood samples. We identified a single nucleotide change (C438T) in the SUMO4 gene using an amplification refractory mutation system (ARMS) technique. To validate the ARMS technique, we compared its results to the results of direct sequencing in 20 subjects. HLA-B51 status was determined by polymerase chain reaction sequence-specific primers.
Results: The presence of papulopustular lesions (p=0.006) and vascular involvement (p=0.045) was significantly different between C438T genotypes in HLA-B51-positive patients with BD. There were no differences in alleleic or genotypic frequencies of the SUMO4 C438T polymorphism between patients with BD and controls (p=0.567 and p=0.818, respectively). The difference in papulopustular skin lesions between CC and CT+TT genotypes in HLA-B51-positive patients with BD was also statistically significant (p=0.002, OR=23.40, 95% CI: 2.33-235.54).
Conclusion: The C438T polymorphism in the SUMO4 gene is associated with significantly increased risk of papulopustular skin lesions in HLA-B51-positive patients.

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SEVERE HEART INVOLVEMENT IN ANTI-KU-ANTIBODY POSITIVE SSC/PM-OVERLAP

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Introduction: Ku-protein is a heterodimeric constituent of the nuclear DNA-dependent protein kinase participating in DNA repair, DNA regulation and gene transcription. Albeit present in a very small subgroup of SSc-patients, in those, Ku is often the only specificity demonstrable at high antibody titre. In European and Japanese patients anti-Ku is present in SSc-PM-Overlap, in US patients mostly in SLE/PM-Overlap.
Case report: In 2006, a 32 year old male patient presented with rapidly progessing diffuse skin sclerosis, severe Raynaud's phenomenon, myalgia, dysphagia and mild arthritis. ANA were positive (>1:2560) with anti-Ku as sole specificity. CK elevated at 1991 U/l, minor interstitial lung fibrosis and no proteinuria. Cyclophosphamide (six monthly boli of 0,75g/m^2 and daily low dose prednisolone) induced partial remission of fibrosis (mRSS: 37). Myositis, however, was unchanged. Concomitant therapy included aspirine, captoprile, nifedipine and physical therapy. A consolidating treatment with methotrexate and two doses of Rituximab was given. Myositis exacerbated, and CK-MB and Pro-BNP became pathological. Methotrexate switched to mycophenolate mofetil. In summer 2008 cachexia and decompensated restrictive left ventricular insufficiency with intermittent AV-block (Wenckebach)

necessitated frequent hospitalisation. Myocardfibrosis was diagnosed bioptically. Because of therapy-refractive myocardial insufficiency NYHAIII, heart transplantation was performed in the young patient in January 2010. Under tacrolimus, mycophenolate mofetil, low dose steroids, and reduced cardiac medication the patient recovered uneventfully to good cardiorespiratory performance and normal values for CK.
Conclusion: Heart involvement in SSc may progress rapidly to incapacitating insufficiency in patients with concomitant myositis as in this Ku-positiv SSc/Pm-Overlap-patient. Heart transplantation is an option.

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REFRACTORY WEGENER´S GRANULOMATOSIS WITH A VERY GOOD RESPONSE TO RITUXIMAB (MABTHERA) AND CYCLOSPORIN A

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Wegener's Granulomatosis is a necrotizing granulomatous vasculitis of small and medium-sized vessels usually affecting the ear, nose, throat tract, lungs, and kidneys. It is characterized by the presence of antineutrophil cytoplasmic antibodies (cANCA) against proteinase 3 which probably mediates the small vessels vasculitis.We report a case of severe form of Wegener's Granulomatosis refractory to the conventional therapy. A 16-year-old boy was admitted to our clinic with presentation of arthralgia, myalgia and vascular hemorrhagic diathesis. After admission he revealed a profound bleeding from gastrointestinal tract and hematuria which caused a haemorrhagic shock. Within the next days a bleeding into the lungs, kidneys and skin appeared. Abdominal pain, ulceration of the oral cavity and nasal septum were also presented. He revealed pulmonary and renal insufficiency. The laboratory tests showed elevated ESR, C-reactive protein, creatinine level and liver enzymes. cANCA titer was 1:160. He underwent exploratory laparotomy and 5 cycles of plasmapheresis. Although the treatment with cyclophosphamide pulses and corticosteroids was managed the disease maintained still active with renal insufficiency and nephrotic syndrome. The treatment with Rituximab was initiated. After 2 infusions of Rituximab, followed by constant treatment with Cyclosporin A the kidney fuction improved and the disease remission was achieved.A combination of Rituximab and CyclosporinA is a promising effective therapy in the treatment of Wegener's Granulomatosis. The patient remains disease free since April 2009 on Cyclosporin A and low dose of corticosteroid.

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HYPERTROPHIC PACHYMENINGITIS – A CLINICAL CASE REPORT

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Hypertrophic pachymeningitis (HP) is a rare disorder characterized by meningeal thickness that can be idiopathic or caused by infection, tumoral infiltration or inflammatory disorders.We report a case of a 61 year old woman who had been diagnosed a p-ANCA associated vasculitis some months before. She presented later in our hospital with headache and vertigo. The patient was submitted to extensive investigation without evidence of any underlying disease. Cranial magnetic resonance imaging (MRI) revealed diffuse dural thickness. A meningeal biopsy was performed and showed unspecific inflammatory process with fibrosis of the dura, compatible with hypertrophic pachymeningitis. This case, as others in literature, suggests that idiopathic hypertrophic pachymeningitis (IHP) might be an autoimmune disorder localized in the meninges.

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DIFFUSE ALVEOLAR HEMORRHAGE COMPLICATING MIXED CONNECTIVE TISSUE DISEASE

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Diffuse alveolar hemorrhage (DAH) is a potentially life-threatening condition that may affect patients with a variety of systemic autoimmune disorders. We report a MCTD patient (Kazukawa's criteria, 1987) with diffuse alveolar hemorrhage after 13 years of disease. This 51-year-old white female with polyarthritis, sclerodactyly, myositis, interstitial lung disease and anti-RNP antibody titers 1/204,800 was admitted to Clinics Hospital of the University of São Paulo with 24 hours of dyspnea and hemoptysis. She had been clinically stable for the last 3 years, taking 10mg of prednisone, mycophenolate mofetil 2g/d and chloroquine diphosphate 250mg/d and rapidly evolved to acute respiratory failure. Orotracheal intubation was needed and tracheal bleeding was noted. There was no history of fever or chest pain. Diagnosis of DAH was made based on drop of hemoglobin levels (11.4 to 6.0 g/dL) and on diffuse alveolar pattern seen on the chest X-ray. There was further evidence of disease activity demonstrated by hypoalbuminemia, lymphopenia, elevated C-reactive protein and creatine kinase levels and low platelet count. ANCA, anti-dsDNA and anti-Sm antibodies were negative and anti-RNP antibodies were persistently high (1/51,200). She received IV methylprednisolone (12mg/kg/dose) for 3 consecutive days and 1,2g IV cyclophosphamide with a good response. She is now completely recovered after eight months of immunosuppressant therapy.
Conclusion: DAH is a rare and severe complication of MCTD. The treatment should be aggressive and initiated as soon as possible to achieve good response.

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MCTD: SECONDARY SJÖGREN'S SYNDROME AND LUNG INVOLVEMENT

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Objective: To determine the prevalence of Sjögren's syndrome (SS) in MCTD patients based on the American-European Consensus Group (AECG) criteria for SS and to assess its possible correlation with lung compromise.
Methods: Forty-four MCTD patients were evaluated as well as forty-one age and gender-matched healthy controls. Ophthalmologic tests for dry eye were performed in order to diagnose probable or definite dry eye. A classification of its severity was also applied. Salivary gland abnormalities were investigated by scintigraphy. High-resolution computed tomography of the chest (HRCT) and respiratory function tests were also performed. Exclusion criteria were previous or current use of xerogenic drugs or smoking habit.
Results: The mean age of the patients was 44.7±12.4 years (comparable to controls) and mean disease duration was 10.8±7.3 years. Definite dry eye was present in 22% of patients (86% when considering probable dry eye). Sixteen percent of patients had severe dry eye while 70.4% had mild to moderate dry eye. Definite and probable dry eye as well as severe, moderate and mild dry eye presented diagnostic test values statistically significant when compared to the control group (p=0.001). Fourteen patients (31.8%) fulfilled the SS criteria. This group had higher values of TLC (p=0.04) and FEV_1 (p=0.008) than the non-SS group. Interstitial lung disease on HRCT was not different.
Conclusions: The preserved respiratory function in secondary SS patients suggests that the SS characteristic small airway disease does not underlie the pulmonary involvement of this subset of MCTD patients.

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VIRAL INFECTIONS IN NEUROBEHCET SYNDROME

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NeuroBehçet syndrome (NBS) is defined as the presence of neurological symptoms associated with signs and/or with imaging and/or abnormal cerebro-spinal fluid in a patient that fulfils the International Diagnostic Criteria for Behçet Disease (BD), after exclusion of other possible causes. Small vessel disease causes the focal or multifocal intra-axial CNS involvement. Large vessel disease presents with thrombosis of the major cerebral venous sinuses.
The aim of the study was to identify a common viral precipitant or variation in response to a common viral agent that would be associated with BD with or without neurological involvement.
Methods consisted of clinical evaluation of patients with NBD followed in a Neuroinflammation Clinic and the cross-sectional measurement of serum IgG antibodies to EBV, VZV, CMV, Measles and HSV-1 with commercial enzyme linked immunoassays. The control groups consisted of patients with BD and healthy controls.
The results showed that the levels of IgG antibodies to EBV-VCA and VZV were increased in patients with NBS compared with patients with BD, and both were increased when compared with healthy controls. One of the patients with severe

residual neurological disability had increased IgG levels for all viruses except for Measles.
In conclusion, the results indicate that the immune responses to the lytic phase of EBV infection and to VZV infection are associated with NBD. Viral infections are good candidates for environmental triggers of autoimmunity. IgG responses can be dampened by use of steroids in more patients with BD compared with NBS patients.

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RELATIONSHIP BETWEEN CALCIUM CRYSTALS ANALYZED BY SEM AND DISEASE SEVERITY IN KNEE OSTEOARTHRITIS

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Introduction. Osteoarthritis (OA) is a degenerative joint disease, which commonly affects the knee.
Aim of the study. To analyze the relationship between calcium crystals (pyrophosphate dihydrate (CPPD), basic calcium phosphate (BCP) and synovial fluid (SF) characteristics in Knee Osteoarthritis (KOA), and clinical activity score (CAS), radiological score (RS) by Kellgren.
Patients and methods. Seventy two patients with KOA (57 F) underwent arthrocentesis and SF examination by optical light microscopy and scansion electronic microscopy (SEM). All patients were evaluated for disease activity indexes such as WOMAC, Lequesne, VAS and RS by Kellgren. The statistic analysis was made with Mann-Whitney test and Pearson test for correlations.
Results. In all specimens the white cell count (WCC) was ≤500/mm^3. The detection of CPPD and BCP by SEM was positive in 30% of cases. These patients were statistically different from patients without crystals for older age (68±7.7; p=0.001), disease duration (59.5±63.4; p=0.004), WCC (291±168; p=0.04) and RS (2.1±1.1; p=0.04). Comparing specimens positive and negative by SEM, in the group with crystals the bivariate analysis revealed a significant correlation between WCC and Lequesne index (r=0.75; p=0.03), between SF volume and RS (r=0.45; p=0.004). In all patients Womac vs Lequesne (r=0.42; p=0.003), Womac vs VAS (r=0.43; p=0.003), Lequesne vs VAS (r=0.45; p=0.002), RS vs disease duration (r=0.32; p=0.03) correlations were shown.
Conclusions: The presence of calcium crystals seems to be associated with a more severe KOA. Further prospective studies are needed to clarify how these factors influence KOA outcome.

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STUDY OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH SPECIAL REFERENCE TO CLINICAL FEATURES AT PRESENTATION CORRELATED WITH RENAL BIOPSY FINDINGS

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Background: SLE is one of the commonest immunological diseases and renal involvement is one of the most dreaded complications of this disease,which is often diagnosed at a late stage.
Aims and objectives: 1) To document SLE using the American College of Rheumatology criteria.
2) To establish prevalence of renal involvement among these patients who may or may not have overt clinical manifestations of Lupus Nephritis.
3) To try to correlate renal involvement with other systems involvement.
Materials amd methods: We studied 39 patients of SLE with no apparent nephropathy in few patients, based on history and clinical examination, attending the OPD of Medical College Hospital, Kolkata. Apart from different blood and urinary biochemical investigations, renal biopsy with immunofluorescence staining were performed on all these patients, after informed consent.
Inclusion criteria: 1. Patients detected with SLE.
Exclusion criteria: 1. Diagnosed cases of SLE who have been treated with immunosuppressive therapy.
2. Diabetes Mellitus and long standing hypertension.
3. Patients having known chronic kidney disease
4. Terminal malignancy.
5. Chronic ingestion of nephrotoxic drugs.
6. Age <15 years and >50 years.
7. chronic illness or infection like Tuberculosis

Results: The mean age of our patients was 26.1+/_7.9 years with 92.3% of females.69.23% of the patients had protienuria,40.54% had WHO Stage IV nephropathy, and 92.3% had IgG type of immunoglobulin deposition on renal biopsy immunofluorescence studies.
Conclusion: We conclude that renal involvement is both common and early in patients with SLE and this should be meticulously searched to allow timely therapeutic interventions.

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A CONTROVERSIAL CASE OF ACUTE HEPATITIS

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A 46-year old woman developed nausea, painless jaundice and pruritus. She was teetotaller, and reported the frequent use of Herbalife® supplemets over the last two years; other hepatotoxic drugs were ruled out. The diagnosis of esotoxic acute hepatitis was made on the basis of the spontaneous near-normalization of the liver tests after the withdrawal of Herbalife® products. As the patient resumed consumption of Herbalife® supplements, liver tests became markedly abnormal again: bilirubin 13.7 mg/dl, aspartateaminotransferase 1684 U/L, alanine-aminotransferase 1246 U/L, alkaline phosphate 486 U/L, gamma-glutamyl-transpeptidase 116 U/L. Viral markers were absent, ceruloplasmin, alpha-1-antitrypsin, ferritin and immunoglobulin levels were normal. High-titre antinuclear antibodies (homogeneous pattern) and anti-smooth muscle antibodies were detected.
Liver biopsy showed hepatic necrosis with marked lymphoplasmacytic and granulocytic infiltrate (neutrophil and eosinophil) and ductular proliferation. Despite Herbalife® products withdrawal, liver enzymes remained persistently elevated. The patient fulfillled the criteria for a probable diagnosis of autoimmune hepatitis and methylprednisolone (0.5 mg/kg) plus azathioprine (1 mg/Kg) induced the complete normalization of liver tests. Female sex, autoantibodies and a dramatic response to immunosuppression are consistent with autoimmune hepatitis. Liver histology, particularly ductular proliferation and eosinophilic infiltrate, points to the concomitant role played by Herbalife®, a well known hepatotoxic agent, in the pathogenesis of this case of acute hepatitis.

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UNRAVELLING THE PHENOTYPE OF CARDIOVASCULAR INFLAMMATION IN PATIENTS WITH RHEUMATOID ARTHRITIS WITH MAGNETIC RESONANCE IMAGING: THERAPEUTIC BENEFITS OF TNF INHIBITION

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Introduction: Aortic stiffness, an independent predictor of cardiac events and a marker of pulsatile LV afterload, improves with anti-tumor necrosis factor-alpha (anti-TNF) therapy in these patients; however, the effects on determinants of systolic function remain undetermined.
Methods and results: Thirteen subjects (age 42.2±21.1 years, females n=8), eligible for anti-TNF therapy completed paired standardized MRI assessments of aortic pulse wave velocity (PWV), global LV function and deformation (peak systolic strains and twist). After 3-month of therapy (mean difference±SD), there was a reduction in CRP (-32.4±47.8 mg/L, p<0.01), aortic PWV (-0.75±0.32 m/s, p<0.01), LV end-diastolic volume (EDV: -9.7±8.7ml, p<0.01), and increased stroke volume (SV: 5.1±3.8ml, p=0.02). LV rotation rate significantly increased, more pronounced in the apex than in base (rotation rate AP: 4.6±3.7°/sec vs. rotation rate BA: 2.1±2.5°/sec), corresponding with a greater improvement in apical radial strain (eAP: 3.2±2.3 vs. eBA: 2.2±3.2) and total longitudinal strain (eLong: 4.5±4.9). In multiple regression analyses (stepwise), baseline aortic PWV correlated independently with log-transformed CRP and radial apical strain (R2=0.973, p<0.001), whereas, after 3 months of therapy, aortic PWV correlated with radial and circumferential apical and total longitudinal strain (R2 = 0.93, p<0.001).
Conclusion: Inhibition of soluble, bioactive TNF with targeted biologics in RA patients with high-grade systemic inflammation prior to therapy is associated with improvement in aortic stiffness and myocardial deformation. These findings suggest that CV dysfunction in these patients is inflammation-induced and reversible.

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INTRAVENOUS IMMUNOGLOBULIN IN ANTI-RO/SSA ASSOCIATED CONGENITAL HEART BLOCK WITH OR WITHOUT MYOCARDITIS

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Objectives: To evaluate intravenous immunoglobulin (IVIG) for the treatment of congenital heart block (CHB) with or without myocarditis.
Methods: We used IVIG (400 mg/kg/day for 5 days) in 4 fetuses, two with myocarditis and two with atrioventricular (AV) block alternating from II to III degree (incomplete). Two women were treated with dexamethasone 4 mg and 2 with betamethasone 4 mg daily.
Results: Fetus 1 presented with incomplete AV block at 22 weeks that remained unchanged after a single course of IVIG done at 26 weeks; 10 days after the fetus died suddenly *in utero*. Fetus 2 presented with incomplete AV block at 20 weeks, that remained unchanged after a single course of IVIG done at 24 weeks. Fetus 3 presented with a complete AV block at 23 weeks; cardiac contractility was depressed with increased myocardial echogenicity. Echocardiographic features of myocarditis resolved a few days after IVIG done at 24 weeks; the degree of the block remained unchanged, but the ventricular rate raised to 90 bpm. Fetus 4 presented at 28 weeks with a ventricular HR of 56 and myocarditis, pericardial effusion and ascites. IVIG were given at 29 weeks with improvement of ascites, pericardial effusion and regression of myocarditis, while HR was unchanged. Titres of anti-Ro/SSA modestly decreased after IVIG administration (from 140,86 to 137,76 UI/L on average).
Conclusions: IVIG had not a great influence on HR and were not able to revert the heart block, but seemed useful to treat the associated myocarditis.

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AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN PATIENTS WITH CHURG-STRAUSS SYNDROME

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Objectives: Although peripheral nervous system involvement in patients with Churg-Strauss syndrome (CSS) has been well documented, little is currently known about its autonomic part. Autonomic nervous system (ANS) function could be assessed by studying heart rate variability (HRV) since a decrease in HRV parameters has been previously linked with ANS impairment.
Methods: Among a group of 24 CSS patients we chose twelve (4 male, 8 female, aged 40±8.3 years) who were in stages of clinical and laboratory disease remission and showed no cardiac involvement. Twelve age- and sex-matched healthy volunteers served as controls. All participants underwent 24-hour ECG Holter recordings along with 24-hour analysis of time domain indexes (SDNN, SDNNix, pNN50, rMSSD). Additionally, 1-hour analysis of frequency domain indexes of HRV were performed. These included total, ultra-low, very-low, low and high frequency powers (TP, ULF, VLF, LF and HF) as well as LF to HF power ratio (LF/HF).
Results: CSS patients showed markedly decreased HRV parameters in 1-hour frequency domains (TP, HF, LF, VLF) while certain time domain indexes values (SDNNix, rMSSD) merely showed trends towards reduction (Table I). These results were not related to disease duration, eosinophil count, corticosteroids, or past peripheral nerve involvement.
Conclusions: Results obtained from CSS patients show noticeably decreased HRV parameters which suggest ANS dysfunction in addition to peripheral nervous system involvement.

Table I. Heart rate variability parameters in 24-hour ECG Holter monitoring from Churg-Strauss patients and healthy controls.

	HRV parameters	CSS (n=12)	Control group (n=12)	*p*
Calculation from 1-hour period of ECG recordings	TP (msec2)	2038 (1706-2105	3622.5 (2730-7164)	<0.001
	ULF (msec2)	165.5 (159-189)	215.5 (152-275)	NS
	VLF (msec2)	544.5 (499.5-595)	738 (649-1041)	0.016
	LF (msec2)	627.5 (590-783)	1050.5 (844-2024.5)	<0.001
	HF (msec2)	561.5 (417-734.5	1574 (980-4051)	<0.001
	LF/HF ratio	1.1 (0.94-1.45)	0.64 (0.52-0.84)	<0.001
Calculation from entire 24-hour ECG recordings	SDNN (msec)	147.5 (119-158)	164.5 (126-183)	NS
	SDANN (msec)	137.5 (108.5-144)	142 (109.5-149)	NS
	SDNNix (msec)	46.5 (38-50)	57 (45-80)	NS; *p*=0.07
	pNN50 (%)	6.1 (2.6-7.9)	7.39 (4.6-19)	NS
	rMSSD (msec)	29 (25-37)	49 (27.5-90)	NS; *p*=0.08

All values expressed in medians (25-75 interquartile range), SDNN: the standard deviation of all filtered RR intervals in the entire 24-hour recording; SDANN: the standard deviation of the average RRs intervals for all 5 min segments of the analysis; SDNNix: the mean of the standard deviations of all RRs for all 5 min segments of the analysis; pNN50: the percentage of differences between adjacent filtered RRs that are greater than 50 msec for the whole analysis; rMSSD: the square root of the mean of the sum of squares of the difference between adjacent filtered RRs over the lenght of the analysis; TP: total power; ULF: ultra low frequency; VLF: very low frequency; LF: low frequency; HF: high frequency power; LF/HF: the low to high frequency power ratio.

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ABNORMALITIES OF REPOLARIZATION IN ECG IN PATIENTS WITH CHURG-STRAUSS SYNDROME

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Introduction: Cardiac involvement (myocardium eosinophilic infiltration and/or vasculitis) in Churg-Strauss syndrome (CSS) is very common, even in disease remission. Nevertheless, little is known about possible myocardial repolarization abnormalities in CSS which may lead to life-threatening ventricular arrhythmias.
Aim: To evaluate myocardial repolarization by measurement of QT dispersion (QTd) in 12-lead electrocardiograms in CSS.
Methods: QTd in electrocardiograms was calculated in 20 CSS (8 male, 12 female) at the time of initial diagnosis and in disease remission and compared with 20 sex- and age-matched healthy volunteers.
Results: QTd in CSS at the time of initial diagnosis was prolonged in patients with heart involvement (52.2 ms ± 12 vs 34.7 ms ± 10.7 respectively; p=0.007) and this difference diminished after accomplishing remission (41.8±13.9 vs 32.6±10.7 respectively; p<0.05). Patients with heart involvement in remission had shorter QTd than during the initial diagnosis (52.2±12 vs 41.8 ± 13.9 respectively; p=0.002), while the QTd did not change in patients without heart involvement (p>0.05). QTd in CSS patients in remission was prolonged when compared to healthy controls (p<0.05), but stayed in normal range. No correlation was observed between QTd and BVAS, eosinophil blood count, presence of ANCA nor the duration of disease.
Conclusions: The most visible increased QTd was detected in CSS patients with cardiac involvement at the time of initial diagnosis. QTd remained prolonged in remission in all CSS (regardless of heart involvement) when compared with healthy controls.

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ANTIPHOSHPOLIPID ANTIBODIES IN INFLAMMATORY RHEUMATIC DISEASE AND IN CORONARY ARTERY DISEASE

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Introduction: The cause of accelerated atherosclerosis in inflammatory rheumatic diseases has not been fully elucidated yet. In theory, antiphospholipid antibodies (aPL) might play a role by promoting atherogenesis and/or thrombosis.
Objectives: The main aim of the study was to look for associations between coronary artery disease (CAD) and inflammatory rheumatic diseases (IRD) and the occurrence of aPL.
Methods: We used ELISA to detect aPL in 67 patients with CAD and IRD (CAD-IRD group) and 53 patients without IRD (CAD-nonIRD) referred to coronary artery bypass grafting (CABG), and in 32 RA patients without cardiovascular disease and 30 HC.
There were no statistically significant associations between any of the examined aPL and CAD, IRD, and RA diagnoses in unadjusted as well as sex and age adjusted analyses.
Conclusion: We did not find any statistically significant difference among the groups in the occurrence of any of the examined aPL. These findings do not support a critical role of aPL in atherogenesis. However, a contribution of aPL to the thrombotic component of atherothrombosis may not be ruled out due to the study design.

Results: Table I.

	CAD-IRD (n=67)	CAD-non IRD (n=52)	RA (n=32)	HC (n=30)	*P* value
Anti-beta 2-glycoprotein I IgG positive- no. (%)	4 (6)	6 (12)	3 (9)	2 (7)	0.763
Anti-beta 2-glycoprotein I IgM positive- no. (%)	3 (5)	2 (4)	4 (13)	1 (3)	0.294
Anticardiolipin IgG positive - no. (%)	8 (12)	4 (8)	3 (9)	7 (23)	0.199
Anticardiolipin IgM positive - no. (%)	3 (5)	1 (2)	1 (3)	0	0.753
Age - years	67±10	68±10	58±10	57±9	<0.001†
Males - no. (%)	42 (63)	34 (65)	8 (25)	17 (57)	0.001

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QRISK AND SCORE ALGORITHMS IN THE ASSESSMENT OF CARDIOVASCULAR RISK IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND FIBROMYALGIA (FM)

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Introduction: Traditional risk factors (TRF) only partially explain cardiovascular risk (CVR) in SLE. Nevertheless, monitoring of TRF is recommended.
Aim: to evaluate CVR based on TRF assessment SLE as compared to FM by the QRISK and SCORE algorithms.
Patients and methods: CVR was assessed by QRISK and SCORE in 40 SLE patients (age 33-69 years, 36 F and 4 M), and in 40 age- and sex-matched FM patients. Both algorithms estimate risk based on gender, age, smoking, systolic blood pressure (SBP) and cholesterol levels. QRISK evaluates also BMI, and can be refined according to additional RF. SCORE estimates only fatal events, QRISK fatal and non-fatal events.
Results: mean age (47.15 vs 47.63 yrs, p=0.839), SBP (127.93 vs 124.75 mmHg, p=0.445), HDL Cholesterol (61.28 vs 60.28 mg/dL, p=0.785), BMI (23.77 vs 25.30, p=0,122), antihypertensive treatment (6/40 vs 10/40, p=0,239), and smoking (12/40 vs 13/40, p=0.809) were not different in SLE and FM. Total cholesterol (217.40 vs 189.05 mg/dL, p=0.009) was higher in FM. QRISK (median 1.8% vs 2.4%, p=0,985), and SCORE (1% vs 1%, p=0.828) ten-year CVR were similar in SLE and FM, while QRISK estimates were not different from average risk of the reference population (median 1.6%, p=0.862 and 0.758 respectively).
Conclusions: CVR is similar in SLE and fibromyalgia, based on TRF evaluation by QRISK and SCORE algorithms. In both diseases, CVR is not significantly different from the general population.

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PRO-ATHEROGENIC CHEMOKINES IN RHEUMATOID ARTHRITIS PATIENTS WITH HYPERCHOLESTEROLEMIA

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Background: The role of chemokines in the pathogenesis of CVD (coronary heart disease, arterial hypertension) and rheumatoid arthritis (RA) is fundamental.
Objective: The aim of the study was to assess correlation of pro-atherogenic chemokines (CX_3CL1, CCL2, CCL5) with lipids concentrations and disease activity in RA patients with hypercholesterolemia (total cholesterol > 200 mg/dl).
Methods: The following data were collected in 58 RA patient (93.1% female): tender (TJC) and swollen (SJC) joint count, CRP, DAS28, Health Assessment Questionnaire (HAQ), total cholesterol (TC), LDL- and HDL-cholesterol, triglycerides (TG), BMI and atherogenicity index (AI). Serum concentration of chemokines - CX_3CL1, CCL2, and CCL5 were measured using ELISA. Data were analyzed using t-tests and Pearson correlation.
Results: Weak negative correlations between CCL5 and TJC (r=-0.29, p=0.044), SJC (r=-0.38, p=0.006) and HAQ (r=-0.30, p=0.030) were found. Positive correlations between CCL5 and AI (r=0.25, p=0.068) and TG (r=0.25, p=0.075) were on the edge of statistical significance. Higher serum concentrations of CCL2 (256 vs 191 pg/ml, p=0.024) was found in patients with CVD. The tendency to lower CX_3CL1 (1405 vs 2450 pg/ml, p=0.050) was observed in patients with BMI >25.
Conclusions: High inflammatory state in RA may influence the role of chemokines in the pathogenesis of atherosclerosis. From the chemokines under study CCL5 was associated with pro-atherogenic lipid profile and negatively correlated with clinical, but not laboratory markers of disease activity.

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SUBCLINICAL ATHEROSCLEROSIS IN PSORIATIC ARTHRITIS: STUDY OF PREVALENCE AND RISK FACTORS IN 41 PATIENTS AND 41 HEALTHY CONTROLS

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Increased cardiovascular morbidity and mortality have been observed in several rheumatic diseases, like psoriatic arthritis (PsA), in which an increased risk seems related to circulatory causes.
Aims: To evaluate the risk factors for subclinical atherosclerosis in PsA patients.
Methods: 41 PsA patients and 41 healthy subjects were evaluated for intima-media thickness (IMT), flow-mediated dilatation (FMD) and endothelial independent dilatation (GTN), using carotid duplex scanning. IMT values were expressed as IMT mean (cumulative mean of all the IMT mean in every analysed carotid segment) and M-MAX (cumulative mean of all the higher IMT in every analysed carotid segment). Subclinical atherosclerosis was correlated with age, body mass index (BMI) and blood pressure in both groups, with duration of arthritis, psoriasis, erythrocyte sedimentation rate (ESR) in PsA patients.
Results: IMT mean and M-MAX were both significantly higher in PsA patients compared with controls (0.7±0.15 vs 0.62±0.09 mm; p<0.01 and 0.86±0.21 vs. 0.74±0.13 mm; p<0.01 respectively). FMD was smaller in patients than in controls (5.9±2 vs 7.5±2.8%; p<0.01). Significant differences in ultrasonographic features between PsA patients and controls were maintained after correction of systolic blood pressure (SBP), the only characteristic differing in the two groups.Univariate analysis showed a correlation between IMT mean and SBP (r=0.217; p=0.05), between M-MAX and age (r=0.392; p<0.001), and BMI (r=0.252; p<0.05), and SBP (r=0.446; p<0.001) in both groups.
Conclusions: We showed that PsA patients exhibited endothelial dysfunctions, which are an early marker of subclinical atherosclerosis.

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AUTO-ANTIBODIES DIRECTED TO APOLIPOPROTEIN A-1 (ANTI-APOA-1 IGG) PROMOTE STERILE INFLAMMATION THROUGH THE ENGAGEMENT OF TLR-2/CD14 COMPLEX ON HUMAN MACROPHAGES

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Background: Anti-apoA-1 IgG have been shown to independently predict poor cardiovascular outcome in rheumatoid arthritis and myocardial infarction (MI), to be associated with an unstable atherosclerotic plaque phenotype in humans and mice, and to promote sterile inflammation (SI) by unknown mechanisms. We investigated whether anti-apoA-1 IgG positivity was associated with higher levels of IL-6 and TNF-α in MI patient, and whether they could promote SI by the engagement of Toll-like receptors (TLR) on human monocyte-derived macrophages (HM).
Methods: HM were stimulated with polyclonal anti-apoA-1 IgG and with purified IgG from anti-apoA-1 positive/negative patients (pool ±, n=3) in presence of blocking TLRs antibodies. IL-6 and TNF-α were measured in supernatant and human MI plasma using a multiplex assay. Nuclear translocation of the transcription factor NFkB was detected by indirect immunofluorescence. TLRs involvement was further investigated using Proximity Ligation Assay (PLA), and HEK293 blue TLR-2/-4 conditional models.
Results: MI patients positive for anti-apoA-1 IgG had higher median levels of IL-6 and TNF-α, when compared to patients tested negative (p=0.02, and, p=0.01 respectively). HM experiments indicate that only anti-apoA-1 IgG and Pool+ induced the nuclear translocation of NFkB, and a significant increase in TNF-α and IL-6 production, fully abrogated by blocking CD14, but not TLRs-2,-4,-5. PLA indicated that anti-apoA-1 IgG interacted mostly with TLR-2, and HEK293 blue-2 model confirmed the CD14-dependency of TLR-2 specific signaling.
Conclusions: These results indicate that anti-apoA-1 IgG promote SI by the engagement of TLR-2/CD14 complex on HM, further emphasizing the anti-ApoA1 IgG pathogenic role in cardiovascular disease.

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CARDIOVASCULAR RISK FACTORS IN RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Aim: The aim of our study was to investigate cardiovascular risk factors in patients with autoimmune disorders.
Materials and methods: The study included 170 patients who fulfilled the ACR classification criteria for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), 58 males 34.12% and 112 females 65.88%, age: 20-85 years old (mean 48.2±13.9 years), 40 of them suffered from SLE, 130 from RA. Controls were 30 individuals matched on age and without systemic autoimmune and cardiovascular diseases. All patients and controls individuals were assessed for the presence of Framingham CHD risk (hypertension, hypercholesterolemia, low HDL, diabetes and smoking).
Results: In comparison with the age- and sex-matched control group, patients with both RA and SLE showed a higher frequency hypertriglyceridaemia (45% versus 15%, $p<0.001$), hypertension (45% versus 10%, $p<0.001$), significantly lower HDL levels (45.3 mg/dl vs 38 mg/dl $p<0.05$) and a lower frequency of smoking (19% versus 31%, $p<0.001$). Some differences in CV risk factors were found between SLE and RA, with hypertension being more common in SLE patients. Although hypercholesterolemia was more frequent in RA ($p<0.005$) and SLE patients display a more atherogenic lipid profile, with significantly lower HDL levels (40.5 mg/dl vs 36.2mg/dl). However, the estimated 10-years Framingham CHD risk score was comparable in both diseases.
Conclusions: These results suggest that cardiovascular risk factors should be taken into account in the management of patients with systemic autoimmune diseases and show the importance of recognizing and controlling risk factors.

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PROGRESSION OF RHEUMATOID ARTHRITIS IS RELATED TO IRREVERSIBLE SYSTEMIC TH1 DEFECTS

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Aims: Distribution of peripheral blood (PB) Th1, Th17 and Treg cells in patients with rheumatoid arthritis (RA) before and after therapy with methotrexate (MTX) and infliximab (IFM) was examined.
Methods: Thirty-six RA patients and 15 healthy controls were enrolled. Patients had been orally taking stable dose of MTX for minimum 6 months before inclusion in study. Sixteen patients had shown clinical response to MTX (MTX group). The other 20 had exhibited unsatisfactory response and remained with active RA; they were qualified for treatment with infliximab in monotherapy or in combination with MTX (IFM group). We examined IFN-gamma, IL-17, and FoxP3 expression in PB CD4+T cells by flow cytometry before and after treatment for minimum 4-6 months.
Results: Before treatment, analysis of Th1 (CD4+IFN-gamma+), Th17 (CD4+IL-17+), and Treg (CD4+FoxP3+) T cells distribution in PB revealed similarly increased Th17 population in both groups of patients. Intracellular IL-17 content depended on RA activity and was highest in IFM group. In RA patients, Th17/Th1 ratio was inverted. In IFM group, we showed decreased Th1 and Treg populations compared to MTX group and controls, accompanied by impaired function of Tregs. After therapy, Th17 and Treg populations were normalized. In MTX group, increased spontaneous IFN-gamma production in CD4+T cells was found. IFM group remained with lower Th1 population compared to MTX group and controls.
Conclusions: Our study confirms expansion of Th17 cells in active RA. Progression of RA results in systemic imbalance of Th1, Th17, and Treg cells, of which Th1 defects seem to be irreversible.

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DIAGNOSTIC EVALUATION OF ANTI-CCP AND ANTI-MCV ANTIBODIES IN DIFFERENTIATING EARLY RHEUMATOID ARTHRITIS

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Objective: Rheumatoid Arthritis (RA) is an autoimmune inflammatory joint disease with systematic complications. The cyclic citrullinated peptide (anti-CCP) antibodies and the mutated citrullinated vimentin (anti-MCV) antibodies are two of the recent serum tests. For this purpose, we will evaluate the diagnostic and prognostic value of these markers.
Material and method: In 197 patients of the Rheumatology Clinic of our hospital with early Rheumatoid Arthritis and in 14 random patients, all of which had RF positive, the serum anti-CCP and anti-MCV levels were measured. From the 211 patients there were 158 female and 53 male. The antibodies of all patients were measured with ELISA method.
Results: From the 211 patients with RA, 160 (76%) had high levels (positive) of anti-CCP. Positive anti-MCV were detected in 155 patients (73,5%). 46 persons had both tests negative, while in 150 patients (71%) there were found positive both anti-CCP and anti-MCV antibodies.
Conclusion: CCP and MCV antibodies are both very useful markers for the diagnosis and the course of treatment of patients with RA. They have similar sensitivity, however CCP appears to have better specification. Their combination seems to increase the diagnostic and prognostic value.
The existence of sensitive specific laboratory tests during the early stage of the disease, when all the clinical signs haven't appeared yet, is of great importance.

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ROLE OF MCVANTIBODIES IN DIFFERENTIATION OF RHEUMATOID ARTHRITIS PATIENTS FROM CHRONIC HEPATITIS C INFECTION PATIENTS WITH ARTICULAR MANIFESTATIONS

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The aim of the study was to determine the value of anti modified citrullinated vimentin (MCV) antibodies in distinguishing Hepatitis C virus (HCV) infection patients with articular manifestations from RA patients.
Subjects and methods: We studied 20 RA patients (HCV -ve), 20 chronic HCV infection patients with articular manifestation and 20 chronic HCV infection patients without articular manifestations. All patients were negative from HBV infection. All patients included in the study were subjected to routine thorough history taking, musculoskeletal examination, laboratory investigation immunological study including anti MCV antibodies by ELISA technique.
Results: There was a statistically significant high levels of anti MCV antibodies in RA patient compared with hepatitis C infection patients with or without articular manifestations. ($f=24.32$, $p=0.0001$).
Nineteen RA patients (95%) were anti MCV positive and only one case (5%) in each group of hepatitis C infection patients were positive for anti MCV antibodies.
Conclusion: This indicates that anti MCV antibodies can be helpful in discriminating RA patients from chronic HCV infection patients with articular involvement.

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TRANSFORMING GROWTH FACTOR B-1 GENE (T 869 C) POLYMORPHISM IN RHEUMATOID ARTHRITIS: ASSOCIATION WITH DISEASE SEVERITY

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Aim of the work is to investigate the possible association of polymorphism in (TGFb1) gene with the disease severity in rheumatoid arthritis. The study was conducted on 50 patients with rheumatoid arthritis (group I) They were divided according to the activity of the disease (Ritchieis articular index-RAI- and ESR) into:
Active group (group A): 29 RA patients.
In-active group (group B): 21 RA patients 15 healthy volunteers (group II) as controls.
All subjects in the study were subjected to : history taking: clinical examination . Routine laboratory and ratiographic investigations, including CBC, ESR. Serological investigations, including rheumatoid factor, Rose-Waaler, (anti CCP). Molecular detection of TGF b1 (T869C) polymorphism (ARMS-PCR).
Results: ESR, RF, RW, anti-CCP were significantly higher in Group I than that observed in Group II. There was a significant positive correlation between the results of RF, RW, anti-CCP and the parameters of disease activity; there was highly significant difference between X-ray findingsand RF, RW, anti-CCP, but was no significant difference between extra-articular manifestations and the results of RE and RW, while there was a significant difference with the results of anti-CCP. No significant difference was detected between the TGFB1 (T869C) and any studied parameter. we can conclude that. Anti-CCP measurement can be considered useful in clinical practice in evaluation of both disease activity and severity of RA. The TGF-b1 gene polymorphism showed no significant association neither with RA nor the prediction of the disease activity or severity.

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CD95 AND BCL-2 EXPRESSION AS APOPTOTIC MARKERS IN RHEUMATOID PATIENTS

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Background: D95 as a death receptor and Bcl-2 as an antiapoptotic protein are among the factors responsible for controlling lymphocytes apoptosis.
Aim of the work: to assess the expression of CD95 and Bcl-2 in PBMNs in RA patients and correlate them with RA activity and functional capacity of RA patients.
Materials and methods: 20 RA patients and 10 healthy controls were included in this study. . All patients were examined clinically and disease activity score (DAS) was calculated for each patient. HAQ was also determined. CD95 and Bcl-2 expression on the PBMNC were assessed by flow cytometry in patients and controls, in addition to CBC, RW test and ESR. Plain X-ray for both hands was also performed for all patients to detect joint erosions.
Results: The mean CD95 expression on PBMNC was significantly higher in RA patients compared to healthy controls (t=3.222, p=0.004). CD95 was also significantly and positively correlated with RAI, (DAS) and (ESR) (r=0.463, r=0.736, r=0.542 respectively and p<0.05 for all). There was no statistically significant difference regarding the mean expression of Bcl-2 in RA patients and controls (t=0.122, p>0.05). It did not also correlate with any of the studied variables.
Conclusion: Increased CD95 expression on PBMNC in RA patients seems to be related to the inflammatory process in rheumatoid disease rather than to the apoptotic process as it is correlated with disease activity measures of the studied patients. Moreover, the normal expression of Bcl-2 in PBMNC indicated that the possibility of dysregulation of apoptosis in this study is unlikely.

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NEW HORIZONS FOR JOINT PROTECTION IN RHEUMATOID ARTHRITIS UNDER ANTI-TNFS: FOCUS ON COMP LEVELS

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Introduction: Recent advances in understanding the role of anti-TNFs in limiting tissue damage have suggested new horizons in the management of rheumatoid arthritis (RA)**.**
Aim: To investigate serum cartilage oligomeric matrix protein (COMP), a tissue-specific non-collagenous protein reflecting cartilage turnover, in RA under TNF inhibitors.
Patients and methods: Prospective observational study on 56 consecutive RA (ACR 1987 modified classification criteria), moderate to severe active forms, treated with 40 mg adalimumab (ADA), twice monthly. Assessments were done at baseline and 12 months according to a predefined protocol, including serum COMP levels and several RA-related such as biological parameters (inflammatory and immune syndrome - rheumatoid factor, anti-CCP antibodies), radiological damage (modified Sharp score) and composite indices reflecting disease activity (DAS28), functional impairment (HAQ-DI) and therapeutic response (EULAR). Statistical analysis was performed in SPSS-17, p<0.05.
Results: Statistically significant decrease in serum COMP has been demonstrated after 12 months of ADA (p<0.05); besides, lower COMP at baseline has resulted in significant higher EULAR response (>75%) independently of the state of systemic inflammation. Statistically significant correlation between COMP and anti-CCP (r=0.81), disease activity (r=0.89), disability (r=0.76), radiological damage (r=0.85) (p<0.05); uni- and multivariate regressive analysis (ANOVA, t-Student, p<0.05) suggest that COMP represent as a effective predictor for rapid and sustained clinical response to ADA, as well as cartilage protection.
Conclusion: Adalimumab is effective for cartilage damage protection in active RA, while COMP levels act as predictive biomarker of treatment efficacy in RA patients under biological agents.

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TARGETING VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) IN RHEUMATOID ARHTRITIS (RA)

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VEGF is thought to play a significant role in RA. In a hypoxic milieu such as the inflamed joint, VEGF secretion is upregulated. VEGF is mainly produced by endothelial cells, fibroblasts and macrophages and exerts its biological activities by binding to its receptors (VEGFRs and neuropilin). Specifically in RA, VEGF i) provokes angiogenesis and stimulates vascular permeability which supplies oxygen and nutrients in the inflamed synovium and also induces chemoattraction of peripheral leukocytes, ii) upregulates cytokines secretion such as TNF-α and IL-6 maintaining and aggravating chronic inflammation and iii) leads to synovial hyperplasia preventing synoviocytes from undergoing apoptosis. Hyperplastic synovium leads to more VEGF secretion in a self-perpetuating cycle.
Several drugs used in RA treatment are shown to downregulate VEGF expression in many reports. Therefore, targeting VEGF is thought to be a promising therapeutic approach in controlling RA. Specifically blockade of VEGF at various molecular biochemical pathways includes i) inhibiting VEGF secretion, ii) blocking circulating VEGF from binding to its receptor with antibodies, aptamers and fusion proteins, iii) blocking VEGF receptors, thus VEGF cannot bind to them and iv) interrupting intracellular VEGF signaling via inhibition of VEGF receptor tyrosine kinase activity.
Further studies are required before these treatments can be used in RA.

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B CELL DEPLETION THERAPY INDUCE AN IMPROVEMENT ON THE QUALITY OF LIFE AND A STEROIDS SPARING IN RHEUMATOID ARTHRITIS

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To evaluate the correlation between improvement of HAQ scores and steroids sparing with rituximab (RTX) treatment in patients with RA.
Methods: 304 patients with active RA were treated with RTX after DMARDs or anti-TNF therapy failure. All of the patients who had received at least one cycle of RTX was studied. Disease activity at baseline and after six and 12 months was assessed using the DAS28, and quality of the life was evaluated by HAQ.
Results: The analysis included 304 patients on database, of whom with established RA [F 255 (83.89%); M 49 (16.12%),]. At baseline, 213 patients (70,07%) were receiving corticosteroids (mean dosage 7.35 mg, range 5-25 mg), baseline DAS-28 values was 6.06±1.21 and HAQ score available in 284 was 1.67±0.69. At 6-month, evaluation was available in 219 patients; a HAQ improvement was seen in 165/219 (mean HAQ decrease -0.69±0,52; p<0,05) the tapered in steroids dosage was seen in 117/213 (mean steroids decrease -0,32±0,48 p<0,05). At 12-month evaluation was available 116 patients; a HAQ improvement was seen in 105/116 (mean HAQ decrease -0,94±0,71, p<0,05) and the tapered in steroids dosage was seen in 16 (mean steroids decrease-1,51±0,78, p<0,05) and in 3 was stopped. A significant correlation was found between number of the cycles of RTX, HAQ improvement and corticosteroids sparing (p=0.047).
Conclusion: This study showed that in "real life" RTX therapy in RA patients improves the HAQ scores and inhibits the use of steroids.

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SERUM LEVELS OF ASYMMETRIC DIMETHYLARGININE AND APELIN AS POTENTIAL MARKERS OF VASCULAR ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS

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Impaired endothelial function represents the early stage of atherosclerosis, which is typically associated with systemic inflammatory diseases like rheumatoid arthritis (RA). As modulators of endothelial nitric oxide synthase, asymmetric-dimethylarginine (ADMA) and apelin might be measured in RA patients to detect early atherosclerotic changes. We conducted a prospective, case-control study to investigate serum ADMA and apelin profiles of patients with early-stage RA (ERA) before and after disease-modifying antirheumatic drugs (DMARDs) therapy.
We enrolled 20 consecutively diagnosed, treatment-naïve ERA patients (mean age 51±14.2, mean disease duration 7.5±9.5) and 20 age- and sex-matched healthy controls. Serum ADMA and apelin levels and the 28-joint Disease Activity Scores (DAS28) were assessed before and after 12 months DMARDs treatment.
In the ERA group, ADMA serum levels at baseline were significantly higher than control (0.55±0.03 *vs* 0.41±0.02 ± mmol/l; p=0.007) and significantly decreased after treatment (0.38±0.03 mmol/l; p=0.012 vs. controls). Baseline serum apelin levels were significantly decreased in ERA patients (1.06±0.56 *vs* 4.67+3.0 ng/ml; p=0.0001 vs. controls), but they were not significantly affected by treatment. Moreover, mean DAS28 significantly decreased after treatment (5.0±2.9 at baseline vs 2.9±1.5; p<0.05) but it doesn't shown any correlation with ADMA nor apelin levels. Our patients presented low apelin and elevated ADMA baseline levels, supporting to the hypothesis that endothelial dysfunction in these patients is related to altered NO homeostasis. It is reasonable to speculate that early, aggressive treatment aimed at suppressing the inflammatory response might reduce the progression of endothelial damage.

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THE DEVELOPMENT OF THE INTERSTITIAL LUNG DISEASE IN PATIENTS WITH LATE ONSET RHEUMATOID ARTHRITIS

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Aim: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by synovial inflammation. The disease can be seen at any age. In this study we aimed to investigate the clinical characteristics of RA patients with disease onset age over 65 years.
Methods: The study group consisted of 258 RA patient (69 male, 189 female; mean age: 58.73±1.45 (32-90); mean disease onset age: 48.96±13 (13-82); mean disease duration: 9.68±7.62 (1-39)). All patients fulfilled RA criteria and the cases with the disease onset age over 65 years were selected. The data was analyzed by using SPSS16.0.
Results: 36 patients (14%) were defined as late onset RA. The late onset RA patients were compared with other patients in terms of clinical features and interstitial lung disease was found significantly frequently in this age group (p=0.002,OR:3.28 8,95%CI:1.504-7.181). There was no significant difference in terms of gender. The development of the erosive disease is more frequently (p=0.464,OR:1,307,95%CI:0.638-2 .678). Serositis was 1.5 fold higher in the elderly group (p=0.350,OR:1.54,95%CI:0,619-3, 831). In these patients the frequency of the prosthesis was 2.7 times higher (p=0.07,OR: 2.7,CI:0.892-8.050). RF and anti-CCP positivity rates and titers were similar in both groups. ANA positivity was 8% in late-onset group and 13.2% other group (p=0.310). Higher than 100 mm/h sedimentation rate was in the late onset group higher but not statistically significant (15%vs.6%, p=0.08). Lung nodules were more common in late-onset group (40%vs.29.6%).
Conclusion: Late-onset rheumatoid arthritis patientsmay be a group of higher risk for the development of interstitial lung disease.

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ORAL MEDICINE AND SJÖGREN'S SYNDROME: EARLY DIAGNOSIS,MANAGEMENT AND TREATMENT

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Introduction: Oral Medicine plays an important role in the early diagnosis of oral manifestations of many systemic diseases. Sjogren's syndrome is a chronic autoimmune systemic disease characterized by xerostomia and keratoconjuctivitis sicca (Primary type). Sjögren's syndrome can be also associated with autoimmune Rheumatoid Arthritis (Secondary type).
Objective: To evaluate the role of Oral Medicine in the early diagnosis of Sjögren's syndrome and Rheumatoid Artheritis (RA) from the oral cavity. Patients presentng in the oral medicine clinic and their main complain is xerostomia should be undertaken to deeply clinical examination to their oral mucosa, tongue, teeth, parotid glands and submandibular glands. Any drugs interactions or suspected bacterial, viral and fungal infections in the oral cavity should be included in the differential diagnosis .Interpretations with others systemic signs and symptoms should be evaluated with the laboratories results to achieve the diagnostic critaria for either primary or secondary Sjögren's syndrome associated with RA.
Conclusions: Sjögren's syndrome is a multifactorial disease including oral mucosal symptoms and multiple dental caries.
Recommendations: Oral hygiene, Dental treatment to all carious teeth, Fluoridation to all remaining teeth, Periodontal treatment, with salivary substitute and salivary stimulants, treatment any oral lesions, certain food should be avoided, counsultaion with Opthalmologist, Rheumatologist and Dermatologist.

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DIAGNOSTIC PERFORMANCES OF ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES TYPE IGM, IGA AND IGG IN SYRIAN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: To determine the diagnostic performances of anti-cyclic citrullinated peptide antibodies (anti-CCP) type IgM, IgA and IgG and rheumatoid factor (RF) in Syrian patients with rheumatoid arthritis.
Methods: Blood samples were collected from patients with definite rheumatoid arthritis according to (ACR) criteria in Al Mwasaa University Hospital and Al Assad University Hospital, Damascus, Syria, from December 2007 to December 2008.64 patients with rheumatoid arthritis were included in our study. Anti-CCP IgM, IgA and IgG and rheumatoid factor (RF) were detected using ELISA.
Results: All tests showed no correlation with gender in RA patients.
The sensitivity of anti-CCP IgG was 71.9% and specificity was 100%, Whereas the sensitivity of anti-CCP IgM was 70.3% and specificity was 64%, the sensitivity of anti-CCP IgA was 43.75% and specificity was 100%, RF IgM showed a sensitivity of 70.3% and a specificity of 96%, and anti-CCP IgG prevalence in patients with negative RF was 31.6%.
Conclusions: This study demonstrates that anti-CCP IgG is a highly specific marker for RA and has diagnostic value especially in RF negative patients.
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ARE DOSES OF LESS THAN 5 MG PREDNISONE SUFFICIENT FOR MOST PATIENTS WITH RHEUMATOID ARTHRITIS TO CONTROL OF DISEASE ACTIVITY?

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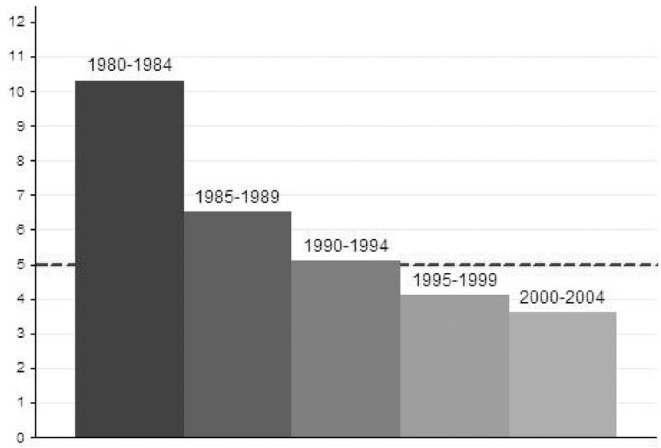
Objective: To compare efficacy of low (<5mg) versus high (≥5mg) dose of prednisone in 308 patients with RA treated between 1980 and 2004, over 12 subsequent months according to change in multidimensional health assessment questionnaire (MDHAQ) scores.
Methods: A database on all patients seen in a rheumatology setting from 1980-2006 includes medications, laboratory tests, and MDHAQ scores at each visit. The proportion of patients whose initial prednisone dose was <5 and >5 mg/day was computed in 5-year periods. Mean changes in MDHAQ scores for physical function (FN) and pain (PN) over 12 months were compared in patients treated with <5 versus ≥5 mg/day.

Results: Mean initial prednisone dose declined from 10.3 in 1980-84 to 3.6 mg/day in 2000-04 (Graph 1).

Mean initial prednisone dose



MDHAQ scores fell by similar levels over 12 months in patients treated initially with < 5 or ≥5 mg/day (Table I).

Table I. Percent clinical change over 12 months.

	Initial dose <5mg/dia	Initial dose <5mg/dia	Initial dose <5mg/dia	Initial dose <5mg/dia	Initial dose >=5mg/dia	Initial dose >=5mg/dia	Initial dose >=5mg/dia	Initial dose >=5mg/dia
Year	N	FN	PN	RAPID 3-EST	N	FN	PN	RAPID 3-EST
FirstSeen								
1980-1984	0	--	--	--	37	+33%	+25%	+28%
1985-1989	3	-5%	-8%	-24%	71	+45%	+42%	+43%
1990-1994	18	+26%	+43%	+38%	59	+44%	+44%	+42%
1995-1999	41	+33%	+30%	+37%	20	+27%	+19%	+25%
2000-2004	51	+37%	+41%	+39%	8	+25%	+25%	+30%
TOTAL	113	+34%	+37%	+37%	195	+40%	+37%	+38%

Most patients were treated with methotrexate.

Conclusion: The mean initial prednisone dose fell by more than 50% over 25-years with increasing use of methotrexate, without differences in efficacy between patients receiving <5 versus ≥5 mg/day.

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CASE REPORT: APPEARANCE OF A RARE DERMATOLOGICAL MALIGNANCY IN A PATIENT RECEIVING ANTI-TNF-ALPHA THERAPY FOR RHEUMATOID ARTHRITIS

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Anti-TNF-α drugs are used in several inflammatory rheumatic diseases, such as rheumatoid arthritis. The increasing incidence of lymphomas in these patients is a well-known data. The greater proportion of the developing lymphomas are derived from the B-cell line, the T-cell lymphomas are more infrequent, especially those, which are involving the skin. The authors report an unusual case of cutaneous T-cell lymphoma in a patient with rheumatoid arthritis receiving etanercept therapy.
The 43-year-old woman diagnosed with RA in 1997 was treated with per os methotrexat and methylprednisolone. Regarding to the ineffectivity of conventional DMARD therapy etanercept was started (Jul-2007). The administration of anti-TNF-α therapy resulted in a remarkable and long-term improvement. In May-2008 on the patient's skin appeared several excavated, reddish skin laesions, which were refractory to the local therapy. In Dec-2009 was performed the skin biopsy, which showed a highly rare form of cutaneous T-cell lymphomas, the subcutaneous panniculitis-like lymphoma. Regarding to the histological result the etanercept was stopped in Mar-2010, the patient was integrated in the dermatooncological care. At present the patient is receiving methotrexat and prednisolon; the disease activity is moderate, the skin laesions are stable, the staging investigations are negative.
The conclusion of this case report is, that there is essential to think about malignancy if a new skin involvement developes during the usage of anti-TNF-α agents, which showed no healing tendency despite of dermatological therapy and due to the histological diagnosis, based on the interdisciplinar approach the patient can be treated adequatly with an effective therapy.

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PERCEPTION OF HEALTH STATUS IN YOUNG ADULT PATIENTS WITH JUVENILE IDIOPATIC ARTHRITIS

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Background: Outcome of juvenile idiopatic arthritis (JIA) is generally regarded as "good", even if many patients have marked functional disability and active disease at 10 years of follow-up. Introduction of anti-TNF modified the course of JIA.
To evaluate quality of life (QOL) in young adults with JIA, using validated measures of functional disability and generic health status.
Methods: 17 JIA patients (>18 years old) switched from a pediatric to an adult rheumatologic setting were evaluated. Functional disability and generic health status/QOL were assessed by the Health Assessment Questionnaire (HAQ) and the Short Form 36-item health profile (SF-36), respectively. SF-36 physical summation score (PSS) and mental summation score (MSS) were considered to reduce the number of comparisons in clinical studies from 8 scales to 2 summary measures.
Results: The 17 JIA patients had a mean age of 18.5±2.3 years, a mean disease duration of 10.7±4.9 years, an HAQ of 0.33±0.31, a DAS of 0.6±0.2. 82.4% were female, 7/17 (41.2%) had active joint disease, 10/17 (51.8%) were under treatment with DMARDs and/or anti-TNF agents.
No differences were observed in health status (PSS and MSS) and in functional disability (HAQ) with respect to disease activity and current therapy. Disease duration correlated directly with PSS (r=0.80, p=0.02) and inversely with MSS (r=-0.74, p=0.03).
Conclusions: Despite good functional indexes and irrespective of disease activity young JIA patients with longer disease duration had worse MSS, suggesting that QOL from a patient's perspective is dependent on a variety of factors, not just physical impairment and functional disability.

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ASSOCIATION OF ANTIBODIES TO CYCLIC CITRULLINATED PEPTIDES AND RHEUMATOID FACTOR WITH C-REACTIVE PROTEIN IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Objective: Evaluate the frequency of autoantibodies against cyclic citrullinated peptides (anti-CCP) and rheumatoid factor (RF) and their correlation with C reactive protein (CRP) in a group of rheumatoid arthritis (RA) patients.
Materials and methods: 70 patients with RA (50 female and 20 male) were included in the study. Serum samples were collected and studied at the time of appointment. RF and CRP concentrations were assessed by nephelometry (BNII nephelometer, Dade Bering, Germany), anti-CCP were measured by ELISA (Euroimmun, Germany). Cut-off values of positiveness were >5 RU/ml for anti-CCP, >5 mg/l for CRP and >20U/ml for RF, as declared by the manufacturer.
Results: Anti-CCP positivity was detected in 51% RA patients, positive RF - in 47% and CRP positivity was observed in 84% RA patients. Significant correlation was detected between anti-CCP and RF (r=0.58, p<0.05). There was no correlation between these autoantibodies and CRP.
Conclusion: Significant association was estimated between antibodies against cyclic citrullinated peptides and rheumatoid factor in a group of rheumatoid arthritis patients. So these autoantibodies may be assessed together as markers of autoimmune disease progression. Data obtained suggest that were no association in the influence of CRP to the development and frequency of anti-CCP and RF.

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BONE MINERAL DENSITY AND BONE TURNOVER IN PREMENOPAUSAL WOMEN WITH RHEUMATOID ARTHRITIS

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The aim of our study was to compare bone mineral density (BMD) and markers of bone turnover in a cohort of premenopausal women with RA and in a group of age-matched healthy women.
The study population includes 65 premenopausal women attending our out-patient clinic for RA and 1.5 folds as many healthy age-matched control women selected from the hospital personnel.
No differences in biochemical markers of bone metabolism between patients and controls were found.

The BMD values at spine and femoral neck were significantly lower in patients with RA as compared with controls with a mean difference of 0.9 and 1.5 T-scores, at the spine and the femoral neck respectively.
When spine BMD values were adjusted for age and body mass index (BMI) the mean T-score differences decreased to 0.84 but it remained statistically significant. The difference between patients and controls decreased when values were adjusted for glucocorticoid (GL) therapy and then for Health Assessment Questionnaire (HAQ) and DAS 28, loosing statistical significance. The difference in femoral neck BMD remained statistically significant after adjustment for age, BMI and cumulative GL therapy (mean T-score difference of 1.1), but lost statistical significance after adjustment for either HAQ or DAS28.
In conclusions, we have shown that low BMD values is a frequent feature also in premenopausal women with RA. The main determinants of this bone loss is disease activity together with functional impairment and then the disease per se particularly at femoral neck.

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SEASONAL AND REGIONAL VARIATIONS IN THE PREVALENCE OF VITAMIN D INSUFFICIENCY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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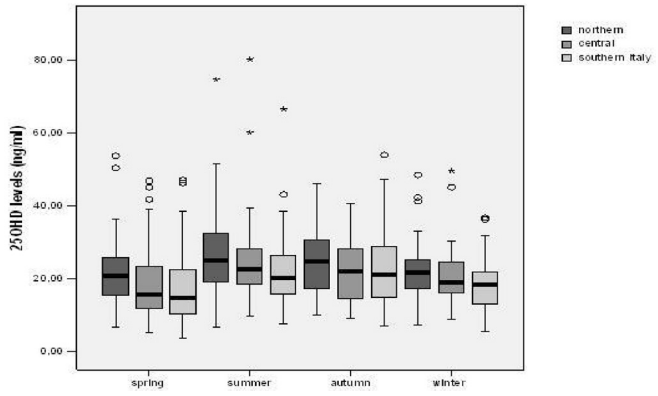
Introduction: In patients with Rheumatoid Arthritis (RA) vitamin D insufficiency is quite common.
Objective: To examine the variability of the prevalence of vitamin D insufficiency in Italy.
Methods: The study population includes 581 consecutive patients (464 women, 117 men; mean age 56 years, range 30-75) affected by RA, not on vitamin D supplements, from 22 rheumatology centres uniformly distributed across Italy (6 northern, 8 central, 8 in southern Italy). All patients were interviewed and examined at each clinical centre for the gathering of information on disease (DAS28, HAQ, ADL) and treatment history. Daily exposure to sunlight from March to September (sun exposure time) was quantified.
Results: the proportion of RA patients with vitamin D insufficiency (25OHD level <20 ng/ml) was 52%. A significant negative correlation between 25OHD serum levels and age was observed.
Significant differences in mean 25OHD serum levels and in the prevalence of vitamin D insufficiency were observed. The highest prevalence was observed in spring and, surprisingly, in southern Italy.

Seasonal and regional variation in 25OHD.
Patients of northern regions had significantly lower BMI, higher sun exposure time



and better indices of disease activity (DAS28) and disability (HAQ, ADL).

Conclusions: Large seasonal and regional variations in the prevalence of vitamin D insufficiency were observed across Italy and these were associated with significant differences in the major determinants of 25OHD levels (BMI and sun exposure time) and in disease activity and disability.

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OCCURRENCE OF LOCALIZED SCLERODERMA (MORPHEA) IN A PATIENT WITH RHEUMATOID ARTHRITIS TREATED WITH ETANERCEPT

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We describe the case of a 54-year-old man affected by rheumatoid arthritis (RA), since the age of 47, with hands morning stiffness, arthritis of the wrists, II, III, IV IFP and MCF and II, III, IV MTF symmetrically and marginal erosions of right IFP II and IV and left IFP III, IV and V at the radiographs. Treatment with corticosteroids, methotrexate and sulphasalazyne was tried without improvement. In september 2005, etanercept was started associated with sulfasalazine. Blood tests showed: ESR 46 mm/h, CRP 18 mg/l, FR and anti-CCP positive and ANA negative. Articular symptoms improved gradually and after 6 months he experienced clinical remission. In December 2008, an erythematous lesion (4 cm diameter) appeared on his back. Blood tests showed ANA 1:320 (speckled) and anti-ENA negative. In July 2009, the skin lesion appeared hyperpigmentated and translucent and a hyperpigmented patch of recent onset in the interscapular region emerge. Skin biopsy documented sclerosis in large clumps of dermis collagen fibres, with inflammatory infiltrate and lymphoplasmacellular epidermal atrophy. The diagnosis of morphea (localized scleroderma) was made and etanercept was discontinued. Systemic and topical corticosteroid therapy with hydroxychloroquine was initiated. Treatment with etanercept was effective in inducing and maintaining remission in RA. TNF-α inhibits TGFβ genes' expression and collagen synthesis by fibroblasts in the skin of patients with scleroderma. The sharp reduction of TNF-α tissue level by etanercept may have altered the relationship between TGFβ and TNF-α and therefore be responsible for developing the framework of localized scleroderma in our patient.

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6Q23 POLYMORPHISM IN RHEUMATOID ARTHRITIS TUNISIAN PATIENTS

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Objective: The aim of this study was to investigate the possible role of the *6q23* region in susceptibility to Rheumatoid Arthritis (RA) in Tunisian patients.
Methods: A case-control study (141 RA patients and 191 healthy controls) was performed with rs6920220 single nucleotide polymorphisms (SNP) witch maps to an intergenic region of *6q23*, between the genes oligodendrocyte lineage transcription factor 3 (*OLIG3*) and tumor necrosis factor-*a*-induced protein 3 (*TNFAIP3*) using Taqman allelic discrimination assay. Data were analyzed by comparison of allelic frequencies, the genotype relative risk and Odds Ratio (OR) with 95% confidence interval (CI).
Results: Our results showed neither allelic nor genotypic significant association of the *6q23* locus with RA (25.5% in RA patients *versus* 22.5% in controls, p=0.35; 45.4% *versus* 39.3%, p=0.26, respectively) (OR $_{(95\%\ CI)}$: 1.18 [0.83-1.70]; 1.29 [0.83-2], respectively). The stratification of RA patients subgroups according to clinical and immunological data did not show any significant association with rs6920220 polymorphism according to the presence of nodules, another autoimmune disease, erosion, anti-cyclic peptides antibodies (ACPA) and rheumatoid factor antibody (RF).
Conclusions: We provided a trend of association of the *6q23* locus with RA in a Tunisian population. These findings have to be confirmed by a replication in largest RA and control groups of the same ethnic origin, increasing the power to detect a true association.

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PHOSPHORUS-BASED DENDRIMER AS NANOTHERAPEUTICS TARGETING BOTH INFLAMMATION AND OSTEOCLASTOGENESIS IN EXPERIMENTAL ARTHRITIS

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Rheumatoid arthritis (RA) is an auto-immune inflammatory disorder characterized by inflammation of the synovial membrane, cartilage degradation and subsequent bone erosion by osteoclasts leading to joint deformation. Therapeutic approaches which have been developed since 15 years are immuno-biotherapies using mainly monoclonal antibodies and soluble receptors neutralizing the effects of cytokines involved in the initiation and development of RA or inactivating B and T cells. Although these biological drugs proved to be efficient, they are very expensive and they fail to cure RA and to inhibit or delay all its deleterious aspects. Thus, innovative chemical molecules that could prevent both the extensive production of pro-inflammatory cytokines and the enhanced differentiation and activity of osteoclasts might represent a real breakthrough in the treatment of RA. Phosphorus-containing dendrimers have been shown to display striking immunological properties towards immune cells. Among these dendrimers, azabisphosphonate-capped dendrimer, called ABP, selectively targets and activates human monocytes toward an anti-inflammatory pathway. Using the IL-1ra-/- mouse model, we have explored the potential of dendrimer ABP for the treatment of experimental arthritis. We have found that dendrimer ABP was efficient to resolve arthritis with a great improvement of synovial hyperplasia and cell infiltration in joints. Serum levels of pro-inflammatory cytokines were taken down to those of normal mice. This anti-inflammatory action was coupled to an anti-bone erosion activity mediated by c-Fms inhibition. Thus, this innovative molecule, which prevents both differentiation and activity of osteoclasts and enhanced production of pro-inflammatory cytokines, might be of great relevance in the treatment of RA.

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ADENOSINE RECEPTORS AND RHEUMATOID ARTHRITIS TREATED WITH METHOTREXATE AND BIOLOGICAL AGENTS

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Background: Growing evidence suggest the involvement of adenosine and its G-protein coupled receptors named as A_1, A_{2A}, A_{2B} and A_3 in the process of inflammation and in Rheumatoid arthritis (RA). Moreover, adenosine receptor stimulation has been shown to have different effects on the release of pro-inflammatory cytokines and some anti-rheumatic drugs may modulate this process.
Objectives: The aim of the present research was to investigate adenosine receptors status in lymphocytes and/or neutrophils from rheumatoid arthritis patients treated with methotrexate (MTX) and biological agents (anti-TNF-α and rituximab) for 1 years.
Methods: Adenosine receptors were analyzed by saturation binding assays and compared with mRNA and western blotting analysis.
Results: Lymphocytes and neutrophils from RA patients exhibited an increased A_{2A} and A_3 density. Analysis of A_{2A} and A_3 transcripts confirms a preferential increase of these receptors in RA patients, suggesting that an altered transcriptional activity and transcript splicing influences their expression. The potency of A_{2A} and A_3 agonists in cAMP production of control subjects and RA patients was investigated and revealed an increase of A_{2A} and A_3 receptor functionality. We found a high density and altered function of A_{2A} and A_3 adenosine receptors that were normalized after anti-TNF-α and rituximab treatment, but not after MTX.
Conclusion: The evidence of A_{2A} and A_3 adenosine receptors involvement in RA treatment, open up the possibility of exploiting their potential role as biomarker in human diseases characterized by a marked inflammatory component.α.

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ASSOCIATIONS BETWEEN SERUM ANTI-CCP ANTIBODY, RHEUMATOID FACTOR AND HLA-DRB1 EXPRESSION IN MOROCCAN PATIENTS WITH RHEUMATOID ARTHRITIS

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Introduction: Rheumatoid arthritis (RA) is a chronic, systemic and inflammatory autoimmune disease of unknown cause. Recently, certain novel autoantibodies have been identified in RA patients. Among these, anti-cyclic citrullinated peptide (anti-CCP) antibodies have strikingly high specificity for RA.
The purpose of the present study was to examine the diagnostic performance of anti-CCP2 and to determine the prevalence of HLA-DRB1 in Moroccan patients with RA.
Methods: Serum levels of anti-cyclic citrullinated peptides antibodies (anti-CCP2), IgM and IgA rheumatoid factors (RF) were measured by enzyme-linked immunosorbent assay in the serum of 64 consecutive RA patients fulfilled the American College of Rheumatology 2010 criteria for RA. Genotyping of HLA-DRB1 alleles was performed by polymerase chain reaction and hybridization with sequence-specific oligonucleotide probes on microbeads arrays. 144 healthy individuals were included as controls.
Results: Of the 64 serum samples 40 (62.5%) were RF positive and of the 47 patients, 32 (68%) were positive for anti-CCP antibodies. The frequency of HLA-DRB1*04 (OR= 2.19), HLA-DRB1*09 (OR= 4.61) and HLA-DRB1* 10 (OR= 2.72) alleles was significantly increased in Moroccan RA patients compared to healthy, not to mention that 90% of the positive HLA-DRB1*04 were women. However in this study we discovered that the HLA-DRB1*07 allele was considerably low in the same population (OR=0.95).
Conclusions: HLA-DRB1*04, HLA-DRB1*09, HLA-DRB1*10 alleles are definitely associated with RA in Moroccan patients, while the HLA-DRB1*07 allele seems to be a protective allele. In addition anti-CCP2 antibodies are useful markers with a sensibility higher than RF in Moroccan patients.

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SUSCEPTIBILITY TO AUTOIMMUNE DISORDERS BY THE LOW EXPRESSION OF CTLA-4 AND PD-1 ON T CELLS FROM SILICA-EXPOSED WORKERS

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Exposure to silica dust has been examined as a possible risk factor with respect to several autoimmune diseases, including scleroderma, rheumatoid arthritis and systemic lupus erythematosus. Given that CTLA-4 molecule [CD152] and PD-1 receptor [CD279] are important for maintenance of peripheral tolerance by regulating T cells activation and tolerance through secondary signals that might influence the activation, inhibition and moderation of T cells responsiveness, we evaluated the CTLA-4 and PD-1 expression levels on the surface of T $CD4^+$ and $TCD8^+$ cells, as well as polymorphisms in the CTLA-4 and PDCD1 genes of 70 silica-exposed workers and 30 non-exposed, age- and sex-matched controls. We observed significant decreases (p<0.05) in the expression of the CTLA-4 on $CD4^+$ T cells of exposed individuals [0.11±0.17% (exposed), 0.28 ± 0.31% (control)] and lower expression (p<0.0001) of PD-1 receptor on $TCD4^+$ [1.98±2.68 (exposed), 6.85±5.85% (control)] and $TCD8^+$ cells [1.53±2.31 (exposed), 6.32±3.38% (control)]. No differences were found between the genotypes in all polymorphisms studied. However, concerning the PD1.3 polymorphism, there was a lower frequency of A allele in the exposed group, which might be associated to the lower expression of PD-1 receptor on the surface of $TCD4^+$ and $CD8^+$ cells. In this regard, comparison of the silica-exposed presenting the type PD-1.3G/G with silica-exposed individuals presenting the PD-1.3A/G genotype showed significantly lower PD-1 expression on $TCD4^+$ cells in individuals carrying PD-1.3G/G. Our findings provide evidence for the association of silica dust exposure and the susceptibility to autoimmune disorders.

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COMPARISON OF 5-HTR3A GENE EXPRESSION CHANGES ON HUMAN PERIPHERAL BLOOD LYMPHOCYTES IN RHEUMATOID ARTHRITIS PATIENTS AND HEALTHY INDIVIDUALS

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Rheumatoid arthritis (RA) is one of the common autoimmune disorders that usually cannot be cured and has substantial personal, social, and economic costs. Although the cause of rheumatoid arthritis is a very active area of research, the etiology of rheumatoid arthritis is obscured. Recent survey revealed that seronongergic system in the central nervous system has been implicated in the etiology and pathogenesis of affective disorders. New evidences have come to light elucidating the modulatory role of serotonin as a neurotransmitter in immune function through the expression of a number of its receptor subtypes in the immune cells. Serotonin receptors genes expression and their alterations in RA diseases have not been reported. We conducted this study to examine whether the 5HT3A receptor gene expression change in RA patients.
Material and methods: In the present study, using RT-PCR technique, the 5-HT3A receptor gene expression was investigated in peripheral blood lymphocyte cells (PBMC) of forty healthy individuals compared to forty RA patients. Each PCR

product of 5-HT3A receptor confirmed by DNA sequencer ABI 3700 capillary system (Applied Biosystem, USA).
Results: The results showed that the 5-HT3A receptor gene is detected on the lymphocytes of both normal control and RA patients. There was a significant difference between 5-HT3A receptor expression profile in RA and that of healthy individuals.
In conclusion: The present study indicated that not only human lymphocytes in normal and patient individuals express 5HT3A receptor, but the expression pattern of 5HT3A receptor gene is different between normal control and RA patients.

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DISEASE ACTIVITY AND ANTI-CYCLIC CITRULLINATED PEPTIDE (ANTI-CCP) ANTIBODY IN SAUDI RF-NEGATIVE RHEUMATOID ARTHRITIS PATIENTS

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Objectives: We investigated the disease activity and prevalence of anticyclic citrullinated peptide (anti-CCP) in Saudi RF-negative R A patients.
Methods: We studied 100 RF-negative RA patients in a private Centre for Rheumatism in Jeddah, K.S.A. All patients met the American College of Rheumatology 1987 diagnostic criteria for RA. Patients with disease duration (dd) ≤1 year (30%) were considered as early RA. Disease activity was assessed by DAS28 scores, anti-CCP was measured by Electrochemiluminescence (Elecsys machine from Roche) and IgM rheumatoid factor was measured by Latex testing.
Results: The 100 RF-negative patients were 73 females, 27 males; with a mean age of 46.5 years (SD=13). Most patients (96%) were receiving disease modifying therapy including methotrexate (29 patients), sulfasalazine (33), hydroxychloroquine (51), prednisolone (15), Leflunomide (Arava) (1), Remicade (1) and combination treatment (30). Prevalence of anti-CCP antibodies in this cohort was 40/100 (40%); and 14/30 (46.7%) in the early RA group. DAS28 scores were low (<3.2) in 2 patients (2 %), moderate (3.2-5.1) in 11%, and high (>5.1) in 87%. There were no significant differences (p>0.10) between positive anti-CCP and anti-CCP negative RA patients for DAS28 and its constituent measures, morning stiffness, CRP, disease duration, and DMARDs. Presence of mixed diseases (30 patient) showed significant correlation (p≤0.01) with anti-CCP positivity; only 6/30 (20%) had positive anti-CCP.
Conclusion: Anti-CCP antibodies are a useful diagnostic tool for RA in RF-negative RA patients from Saudi Arabia. However, they have limited value in predicting disease activity in these patients.

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WEEKLY ORAL CYCLOPHOSPHAMIDE COULD BE AS SAFE AS MTX IN CARING PATIENTS WITH RHEUMATOID ARTHRITIS (A PILOT STUDY)

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Background: Rheumatoid arthritis (RA) is the most common rheumatic disorder word wide. Cyclophosphamide the old drug is highly potent immunosuppressant and is still used as the firs line drug in the most severe rheumatic condition. Concerns regarding this agent is more related to its potential toxicity. Far interval between administering the drugs is a critical issue in minimizing side effects.
Method: We used oral cyclophosphamide (CYC) in doses of 150 mg as single weekly regimen in caring selected cases of RA patients, refractory or ineligible for MTX regimen. 10 cases were followed for a minimum two years. periodic clinical and laboratory investigations were done as patients on MTX. Yearly urine cytology performed for screening of bladder neoplasm.Oral Weekly Mesna also prescribed at bed time at days of oral CYC.
Results: None of the patients had major side effect related to CYC. Only one patient complained of nausea after having the pills on CYC days necessitated discontinuation of CYC. None of them had liver enzyme elevation or renal dysfunction. Clinical response was as good as MTX in other RA patients.Seven patients had favorable response regarding Morning stiffness, joint count, tender and swollen joints.
Conclusion: CYC could be a good substitute for MTX in selected cases of patients who are candidates for MTX therapy.

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ANTI-SA AUTOANTOBODIES FOR RHEUMATOID ARTHRITIS : A GENDER ORIENTED STUDY

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Rheumatoid arthritis (RA) may affect a lot of tissues and organs, mainly threating synovial joints. It is a "gender disease" that strikes 5 times more women than men. Among biomarkers used for early detection, anti-Sa antibodies showed high specificity for the diagnosis of RA.
Sera from a cohort of 110 patients composed of 20 suspect cases and 20 patients afflicted by RA, 15 by SLE, 15 affected by psoriatic arthritis, 20 by mixed connective tissue and 20 healthy donors were tested for the serological research of RF, anti-CCP and anti-Sa.
In this study we evaluated, in a gender perspective, the importance of anti-Sa for their predictive and prognostic value in inflammatory arthritic disease progression.
The results showed that 10 of 20 anti-CCP positive patients resulted positive for anti-Sa, too. Of the men-group afflicted by RA, 60% resulted positive for anti-Sa test while in the women-group positives were 47%. Of 70 patients negative to anti-CCP, 2 (1 with psoriatic arthritis and 1 with mixed connective tissue) were tested positive for anti-Sa, in particular 20% of the male population with psoriatic arthritis and 7.1% of females with mixed connective tissue.
Anti-Sa appear to be an useful biomarker for diagnosis of RA especially in male gender and in man with psoriatic arthritis anti-Sa may represent an index of severity of the disease. The serological anti-Sa dosage is specific for an early diagnosis of RA, while the sensitivity for anti-Sa serological research needs to be reconsidered on a major survey in future studies.

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EVALUATION OF STREM-1IN SERUM AND SYNOVIAL SYNOVIAL FLUID OF CHILDREN WITH JUVENILE RHEUMATOID ARTHRITIS

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Objective: STREM-1 belongs to immunoglobulin super family and secrets by monocytes as part of innate immune system. Initial studies have shown that sTREM level rises in bacterial and fungal infections.Nonetheless, recent studies have shown sTREM-1 rises even in other inflammatory processes.The objective of this study was to determine sTREM-1 level in serum and synovial fluid of children with juvenile rheumatoid arthritis.
Methods: This study was conducted over 27 children with Juvenile rheumatoid arthritis. All of cases needed joint fluid aspiration to be diagnosed or for treatment. sTREM-1 was measured in serum and synovial fluid of these patients and was compared with normal population. Excluding infectious causes, joint fluid was cultured in BACTEC environment. After informed consent, sTREM-1 level was also measured in serum of 27 individual healthy controls.
Results: The average sTREM-1 serum level in patients with juvenile rheumatoid arthritis was 124 pg/ml, and in control group it was 84.5 pg/ml (p value: 0.008). The average of sTREM-1 level in synovial fluid of patients was 160.5 pg/ml. No relation between elevated sTREM-1 levels and other acute phase reactants was detected. Patients with very high level of sTREM-1 in serum experienced recurrences.
Conclusions: Elevated sTREM-1 serum and synovial fluid level is not only attributable to infection but also to other inflammatory processes as like as JRA. The rise of sTREM-1 in serum and synovial fluid were parallel to each other. Children with repeated arthritis recurrences had more elevated sTREM-1 levels. Therefore, sTREM-1 might be a prognostic factor for JRA.

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LACK OF SPECIFICITY OF ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES IN ADVANCED HIV-INFECTION

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Objective: To determine the prevalence and specificity of anti-cyclic citrullinated peptide antibodies (a-CCP) and rheumatoid factor (RF) for rheumatoid arthritis (RA) in human immunodeficiency virus (HIV)-infection and evaluate the effect of immune reconstitution on these markers.
Methods: Patients with advanced HIV-infection without arthritis were enrolled. CD4-counts, a-CCP and RF were determined before initiating anti-retroviral therapy (ART) and repeated after 6 months. Results were compared to those of healthy controls. Patients were reviewed for the development of RA for one year.
Results: Sixty patients and 26 controls were studied. Six-month follow-up results were available on 49 patients. Mean (SD) levels of a-CCP were higher in HIV-infected patients compared to controls: 9.50 (11.41) versus 0.80 (1.32) units (p<0.001). Mean (SD) levels decreased to 4.85 (8.12) units (p=0.006) after 6 months of ART (HIV-infected group). Fifteen percent of patients initially tested positive for a-CCP, 4% after 6 months versus no controls (p=0.031). Forty seven percent of patients initially tested positive for RF, 18% after 6 months versus 8% of controls (p<0.001). Decreases in RF and a-CCP after ART were accompanied by increased mean (SD) CD4-counts: 129 (56) to 278 (140) cells/mm^3 (p<0.001). A-CCP and RF positivity was not associated with the development of RA.
Conclusion: Increased titers of a-CCP and RF occur in advanced HIV-infection. Although more specific than RF, before immune reconstitution, a-CCP is an unreliable diagnostic marker for and does not necessarily predict future RA. After immune reconstitution, the specificity of a-CCP approaches that of a control group.

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WORK-RELATED MUSCULOSKELETAL DISORDERS AND WORKFORCE LOSS

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Occupational diseases are disorders of health resulting from conditions related to the workplace. The problems that ocur concerning with the body system are important in terms of the occured workforce loss and the share of treatment cost in the economy so much as they are important for the worker himself/herself and the employer. Especially musculoskeletal disorders among the other occupational disease are increasing remarkably in both developing and developed countries and they cause heavy burdens on the social security systems. This study aims to define the workforces which are caused by musculoskeletal disorders, the prevalence of which is high in our country, and provide feedback to the patient, employer, state and economy. In this study the data were collected by means of using the measurement which has been prepared for determining the workforce losess in sedentary instructors working in Başkent University and EuroQol 5D, Visual Analogue Scale. 175 of 587 academic staff have participated in this research. After identifying the workforce loss time, the loss values were counted by considering the payrolls of those who work for loss value. Also, the disabilities concerning the life qualities were counted by considering the EuroQol 5D scale. As a result of the analysis, we found that most employees complaints of back and muscle tension, lower back, neck and back pain. In the last one year, the cost of the work-related musculoskeletal disorders calculated 19.000 TL (12.418$) for the Başkent University.

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WHAT ARE THE DETERMINANTS OF PARTICIPATION IN PHYSICAL ACTIVITIES AMONG CANADIAN CHILDREN AND YOUTH WITH ARTHRITIS?

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Aim: To identify the individual and contextual factors that may influence participation in physical activities among Canadian children and youth with arthritis.
Methods: A secondary analysis was completed on the data obtained from the Participation and Activity Limitation Survey (PALS) 2006 data base, a Canadian post-census survey. Parents were interviewed over the telephone and asked about their child's participation and limitations in various activities. We analysed data reported by parents caring for a child aged 4 to 14 years with arthritis. Following proper ethical and security clearance, analysis of data took place at the McGill Laboratory of Quebec's Inter-University Centre for Social Statistics (QICSS), Montreal, Quebec. Correlation analysis was used to examine the associations between individual and contextual determinants with the level of participation in physical activities.
Results: Mobility restrictions (i.e. difficulty walking) and hand restrictions (i.e. difficulty grasping or holding objects) were reported in 36.9% and 34.8% of children with arthritis, respectively. The determinants that showed a significant negative association with participation in physical activities were: the lack of recreational facilities in the community (p=0.007), the high cost of activities (p=0.038) and the child's need for assistance to participate in physical activities (p=0.031).
Conclusion: Policy changes can target the above mentioned individual (need for assistance) and contextual factors (proximity of community services and cost of activities) reported by parents to favour participation in physical activities among Canadian children and youth with arthritis.

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PREDICTORS OF RESPONSE TO TREATMENT WITH ABATACEPT IN PATIENTS AFFECTED BY RHEUMATOID ARTHRITIS

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Purpose of the study: Recently many studies on biological drugs, used against rheumatoid arthritis (RA), have been conducted to identify possible predictor of response to the therapy. Purpose of this study was to look for parameters that can predict the response to Abatacept therapy.
Materials and methods: We examined 16 patients (2 M, 14 F) with RA, treated with Abatacept during 12 months follow up. We considered the numbers of biological drugs used previously, FR, anti-CCP, ESR, RCP values; HAQ score. Disease activity has been evaluated through the DAS44 at the beginning of the treatment (T0), at 3 months (T3) and at 12 months (T12).
Results: Significant differences have been found for HAQ, ESR and RCP. Only patients with HAQ score <1.5 or ESR >20 mm/h or RCP values >5 mg/dl, showed a marked and significant reduction of disease activity (DAS). Interestingly all the patients (8/16) who achieved a moderate EULAR response during the 1 year follow-up reached it at T3 and maintain it at T12.
Conclusion: By data listed above, low values of HAQ and high values of ESR and RCP at the beginning of the treatment proved to be a possible predictor of response to Abatacept. Different Authors reports an increasing Abatacept effectiveness during time, in contrast with these studies, our preliminary data suggest that 3 months therapy seems to be enough to evaluate Abatacept efficacy.

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MONITORING OF SELECTED IMMUNOLOGICAL PARAMETERS IN BIOLOGICAL THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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New knowledge about the immunopathogenesis of rheumatoid arthritis used biological therapy, which attempts to restore the balance between cytokines, T lymphocyte costimulation control, and activation of T lymphocytes or B cell ablation. The goal was to track changes in available immunological parameters of humoral and cellular immunity in the course of biological therapy in patients with RA and find the parameters that were predictive factors for treatment efficacy. We observed changes in T lymphocytes and their subpopulations, B lymphocytes, and NK cells, rheumatoid factor (RF), antibodies against citrullinated peptide (aCCP), anti -dsDNA antibodies and ANA before biological therapy anti-TNF (n=30), anti-CD20 (n=15), anti-IL6 (n=15) and during there therapy.
Changes in representation of basic lymphocyte subpopulations in peripheral blood of anti-TNF therapy were very individual. We have seen an increase in the number of Treg cells already after 1 month of therapy. In the treatment of anti-CD20, we found a significant reduction of B lymphocytes (7.8±4.4% vs 1.0±0.96%). At 80% we recorded the complete depletion of B cells after 1 month of therapy.
For each type of therapy are patients with good clinical effect seen significant decline in levels of RF and aCCP. ANA antibodies during therapy significantly altered.
Representation of the endpoints of memory B lymphocytes in peripheral blood in antiCD20 therapy and monitoring levels of RF and ACCP antibodies at all study treatments was correlated with clinical improvement.

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HOW IMPORTANT IS SMOKING AS A RISK FACTOR FOR RHEUMATOID ARTHRITIS?

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Introduction: Smoking is associated with protein citrullination and a higher relative risk to develop RA in patients with certain shared epitope alleles. Therefore, smoking is regarded as a risk factor for RA development and severity, although conflicting data are reported.
Objective: To analyze smoking for risk for RA and severity in 6,870 patients in the QUEST-RA (Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis) multinational database, from 86 sites in 33 countries.
Methods: Patient smoking status, demographic data, RA Core Data Set and other RA measures, and cardiovascular comorbidity were assessed; significance was analyzed with t tests and chi square, adjusted for age, sex, and disease duration.
Results: 64% of QUEST-RA patients "never smoked," 15% were "current smokers," and 21% "stopped smoking" (Table). Smokers were more likely to have nodules, rheumatoid factor (RF) and/or coronary artery disease (CAD) (p<0.001), but better clinical status versus non-smokers according to all Core Data Set measures and DAS28 (Table).

Table. Smoking history and clinical status in 6870 RA patients.

		Ever smoked			
	Never smoked	Current smoker	Ex-smoker	P never vs ever	P current vs ex-smoker
Number of patients	4.406	1.059	1.405	-	-
% of all patients	64.1%	15.4%	20.5%	-	-
Age (years)	54.9	53.1	58.4	<0.001	<0.001
Rheumatoid factor	71.9%	77.8%	76.3%	<0.001	0.37
Erosions	63.4%	58.7%	61.6%	0.021	0.16
Nodules	17.7%	25.5%	20.9%	<0.001	0.010
Coronary artery disease	6.8%	4.8%	12.1%	<0.001	<0.001
*DAS28 (0-10)	4.4	4.0	4.0	<0.001	0.87
*HAQ-function (0-3)	1.1	0.90	0.93	0.010	0.54
*Swollen joint count (0-28)	4.5	4.1	4.1	0.062	0.76
*Tender joint count (0-28)	7.3	6.0	5.7	<0.001	0.80
*Physician global (0-10)	3.1	2.7	2.6	0.001	0.97
*ESR (mm/h)	32	26	28	<0.001	0.11
*Pain (0-10)	4.2	4.0	3.9	0.28	0.062
*Patient global (0-10)	4.1	4.0	3.8	0.16	0.079

*For Core Data Set variables, analyses adjusted for age, sex and disease duration.

Conclusion: Most people who develop RA never smoked; smokers with RA have more nodules, RF and CAD, but better clinical status in all other measures. Smoking is a risk factor to develop RA in a small patient subset, but not in general in RA.

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DAILY VS. WEEKLY SUPPLEMENTATION OF FOLATE IN RHEUMATOID ARTHRITIS PATIENTS RECEIVING WEEKLY LOW DOSE METHOTREXATE (MTX)

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Introduction: Methotrexate (MTX) inhibits dihydrofolate reductase. In low doses (<20 mg/week), MTX is used as a disease-modifying antirheumatic drug and is indicated for treatment of rheumatoid arthritis. Efficacy of low-dose MTX may be the result of anti-inflammatory or immunotoxic effects. Adverse effects of MTX in patients with RA are related to folate antagonism. Studies found that patients on folate supplementation remained on therapy longer, resulting in "MTX survival" and more durable control of RA symptoms. Studies have shown that folic acid may prevent side effects other than elevated liver-function tests [LFTs].
Objectives: To compare the efficacy of folate supplementation in either preventing or reversing side effects of low dose MTX; namely elevated liver function and anemia, in 148 RA patients.
Methods: We randomly assigned 148 RA patients into 2 groups : group A patients (daily) to receive 5mg folic acid daily tablet after lunch except for the day of the injection, 1 day before and 1 day after AND group B (weekly) patients to receive four 5 mg folic acid tablets at once weekly 2 days post injection after lunch.
Resuts: We found that daily administration of folate is more effective than weekly administration in alleviation of MTX side effects (mainly ↑LFTs) as more patients on the weekly regimen had abnormal liver enzymes (23/67) when compared to the daily regimen (11/81) [p=0.003].
Conclusion: Daily folic acid is more effective than weekly administration in alleviating side effects of low dose MTX (↑LFTs) and should be given at least 1 day post injection.

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OVERWEIGHT AMONG MOROCCAN PATIENTS WITH RHEUMATOID ARTHRITIS

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Objective: To estimate the prevalence of overweight among Moroccan patients with Rheumatoid arthritis (RA) and its correlates.
Methods: 260 patients with RA were included. Disease activity was measured using the disease activity score (DAS28). Radiographic changes were assessed using the Sharp's method as modified by van der Heijde. Functional impairment was assessed by using the Health Assessment Questionnaire (HAQ). Extra articular manifestations, immunological status and treatment details were specified. Overweight was defined according to the Body Mass Index (BMI): Underweight <18.5; normal weight 18.5- 24.9; overweight 25-29.9 and obesity ≥30.
Results: The mean age of patients was 45.53±11.4 years and the mean disease duration was 9.46±8.43 years. 74 patients (28.46%) were overweight, 42 (16.15%) were obese and 144 (55.38%) were normal. Overweight and obesity were associated with prolonged disease duration (r=-0.281), disease activity (r=-0.426), Sharp total score (r=0.297), the rate of rheumatoid factor (r=-0.311) and with the rate of anti-cyclic citrullinated protein antibodies (r=-0.421) (p≤0.01). There were no statistically significant differences in BMI according to gender, presence of extra articular manifestations; functional impairment or treatment with corticosteroids (dose and duration) (p=0.343).
Conclusion: Approximatively more than 44% of our RA patients have a higher weight than normal. Prolonged disease duration, high disease activity, severe structural damage and positivity of rheumatoid factor and anti-cyclic citrullinated protein antibodies are the most correlated parameters with overweight. Overweight seems to be an important issue for our patients with RA and could expose them in addition to their disease to increased cardiovascular risk.

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DO CHANGES IN LYMPHOCYTES SUBPOPULATIONS CAN BE HELPFUL FOR DISTINGUISH PATIENTS WITH UNDIFFERENTIATED ARTHRITIS?

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Patients with undifferentiated arthritis (UA) could develop many types of rheumatic diseases, but the final diagnosis at this stage is very problematic. The aim of our study was to find out if changes in lymphocytes subpopulations could be a good diagnostic strategy for distinguish patients with UA.
We enrolled 37 UA patients into the study. Five ml of peripheral blood was collected at the day of the first rheumatologist visit and activation markers on CD4 cells and CD28 marker on CD4 and CD8 cells were measured by flow cytometry. The final classification of UA patients into different rheumatic diseases groups was based on EULAR criteria, and were done during 1,5-year follow-up observation.
UA patients progressed to psoriatic arthritis (PsA), rheumatoid arthritis (RA), Sjögren's syndrome (SS), ankylosing spondylitis (AK), reactive spondyloarthropathy and rhupus. Some patients were diagnosed with arthritis in the course of autoimmune thyroid disease (AD) and some still remain as UA.
Activation status of $CD4^+$ lymphocyte was the highest in patients with SS. The ratio of percentage of activated T cells to regulatory $CD4^{low}CD25^{high}$ cells was the highest in patients with AK and the lowest with RA. Patients with SS and PsA had the lowest percentage of $CD4^+CD28^-$ compared to patients with RA, AS and rhupus. Rhupus patients had the highest percentage of $CD8^+CD28^-$ cells.
We observed significant changes in activation status of $CD4^+$ lymphocytes and percentage of $CD4^+CD28^-$ and $CD8^+CD28^-$ cells in peripheral blood of UA patients before the final diagnosis, which could be used for earlier diagnosis.

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A CONTINUING CONTROVERSY IN RHEUMATOLOGY – OPTIMAL DIAGNOSIS AND MANAGEMENT OF POLYMYALGIA RHEUMATICA AND ITS LINKS WITH GIANT CELL ARTERITIS

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Introduction: Polymyalgia rheumatica (PMR) was defined in 1957 and is linked with giant cell arteritis (GCA) in approximately 25% of cases.The peak incidence is between 60 and 75 years old and is increasing with the ageing population. Polymyalgia rheumatica is a clinical diagnosis without a 'gold standard' serological or histological test and there are other conditions that may mimic PMR.
Aim: To summarise a review of the literature to provide guidelines regarding diagnosis and treatment.
Purpose: Gaining consensus in a common area of rheumatology within primary care and specialist practice
Methods: Consideration of the overlap betwen PMR and CGA and in particular where temporal arteritis is suspected, how this manifestation of GCA is investigated and it is recognised as a treatable medical emergency to prevent possible blindness. The mainstay of treatment is steroids, usually prednsiolone. Various documented doses are considered for PMR and GCA.
Discussion: Providing management advice where there are no absolute guidelines as to the investigation of this condition or the dose of prednisolone or its duration when the diagnosis is suspected. Similarly, the rate of reduction of prednisolone and its titration depending on the individual's response.
Conclusion: This remains a controversial area of rheumatological practice and it currently is an ongoing challenge requiring further research.

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USING DUAL-ENERGY COMPUTED TOMOGRAPHY FOR THE DIAGNOSIS OF PERIPHERAL AND AXIAL GOUTY ARTHRITIS

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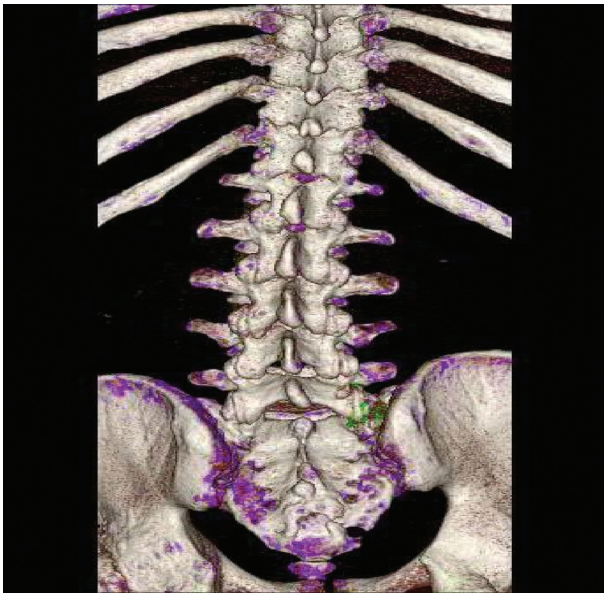
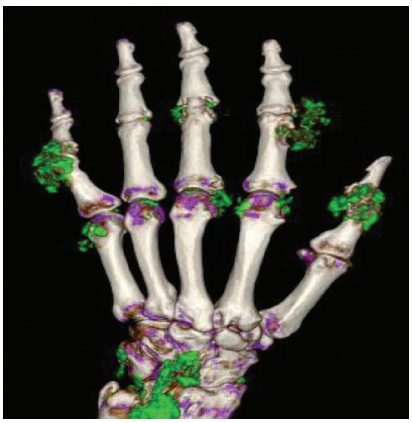
Introduction: Acute gout typically lends itself to prompt diagnosis when occurring in peripheral joints; however, the diagnosis of axial gout is more challenging. Rapid diagnosis is desired since symptoms may include refractory pain and progressive neurological deficits. Dual-Energy Computed Tomography (DECT) is a noninvasive imaging technique that can readily identify the distinctive appearance of tophaceous deposits.
Case report: We discuss 4 cases in which DECT was used to support a diagnosis of tophaceous gout, two describing peripheral gout and two describing axial gout.
One case involves a patient without a previous diagnosis of gout who initially presented with tophaceous axial gout.
Conclusion: Neither plain radiographs, nor ultrasonography, nor MRI has been shown to consistently and specifically reveal gouty involvement of the spine. In patients with back pain and history of gout, DECT may prove useful in the noninvasive diagnosis of axial tophaceous gout and facilitate expedited treatment with the expectation of improved clinical outcome.



Right L5-S1 facet joint tophaceous gout.



Diffuse active gouty arthropathy of the hand.

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POSSIBLE PREDICTIVE VALUE OF CLINICAL FEATURE, SEROLOGY AND IMAGING IN DIFFERENTIAL DIAGNOSIS OF EARLY ARTHRITIS

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When approaching patients with inflammatory arthritis, early differential diagnosis between Rheumatoid Arthritis (RA) and other inflammatory arthritis is mandatory. American College of Rheumatology classification criteria are not fully suitable for very early diagnosis of RA. Disease-modifying antirheumatic drugs and biologic agents, if started early, could change the course of disease. Ultrasonographic (US), clinical and serological (APCA, RF, ESR, CRP) findings are important in the evaluation of early arthritis patients. Aim of the study has been to identify the predictive value of clinical feature, serological biomarkers and US score in a cohort of patients with recent onset arthritis. Between May 2006 and May 2008, 49 consecutive outpatients presenting with undifferentiated arthritis (UA) of less than 12 months of duration were recruited in our Early Arthritis Clinic. Clinical and serological findings were evaluated in each patient; US assessment included bilateral wrist, metacarpophalangeal, proximal interphalangeal of the hands, knee and metatarsophalangeal joints, chosen because commonly involved in RA and reliably assessed by US. Serum levels of IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IFN-γ, MCP-1, MIP-1β e TNF-α were determined. 51% of patients were diagnosed as RA, whereas 49% were still classified as UA. Considering clinical and serological features there was a significant difference in DAS 44 (p=0.003), ESR (p=0.03), RF (p=0.0008), ACPA (p=0.002) and US score (p=0.048) between the two groups. There was no difference in the level of all the cytokines. A complete evaluation which include US score and DAS44 is important for early differential diagnosis of inflammatory arthritides.

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DISABILITY IN PSORIATIC ARTHRITIS PATIENTS: FOCUS ON VICON GAIT ANALYSIS

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Although Psoriatic Arthritis (PsA) was primarily considered to be a benign condition, almost one third of cases develop relatively severe disease, with high disability and socio-economical impact, as suggested by recent reports.
Aim: To evaluate health-related quality of life (Qol) and work disability and to perform a complex biomechanical gait analysis in PsA.
Material and methods: Preliminary prospective study on 33 consecutive polyarticular active PsA (2006 CASPAR criteria). Assessments included rheumatology (activity scores) and dermatology domains (PASI-score); functional disability (Health Assessment Questionnaire, HAQ) and quality of life scores (Short Form36, SF36); biomechanical gait analysis (tridimensional VICON MX optical motion capture system). Data were compared with a control group (number-, age-, sex-matched healthy controls). SPSS-17 was used for statistical analysis (descriptive statistic, non parametrical tests - ANOVA, Spearman rank correlation test), p<0.05.

Results: While the majority of PsA experienced a moderate impact on QoL as assessed by SF36 analysis, severe disease had major impact on physical and emotional health status. VICON gait analysis proved statistical significant change ($p<0.05$) on several gait parameters as compared to controls, including: decreased range of motion for flexion/extension of the lower limbs joins and lower cadence, decreased walking speed and step length. Statistically significant correlations (Spearman, $p<0.05$) between changes in PsA gait parameters and SF36 results, but no association with HAQ ($p>0.05$) have been reported.
Conclusion: The PsA burden is related to both quality of life and work capacity impairment. Severe changes in gait parameters are essentially reflected in SF36 analysis.

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MORPHOMETRIC ANALYSIS OF CAPILLAROSCOPIC IMAGES DURING PSORIATIC ARTHRITIS: COMPARISON WITH RHEUMATOID ARTRHITIS

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Psoriatic arthritis (PsA) is an inflammatory arthropathy associated with psoriasis. Differential diagnosis with rheumatoid arthritis (RA) is based on clinical, serological and radiological criteria. However, an early diagnosis of PsA can be difficult in patients sine psoriasis or with rheumatoid-like involvement. Morphological and rheological alterations of microcirculation has been emphasized in RA and PsA patients. We propose, through morphometric analysis of capillaroscopic images, identification of specific abnormalities associated to these diseases. Morphometric analysis was performed on capillaroscopic images of nailfold district of 20 PsA patients, 20 RA patients and 20 healthy subjects. We measured: average venous, arterial and loop limb diameter, average width of the capillary loop, linear density of capillaries on 2 mm. Measurements comparison showed statistically significant differences in all the parameters examined. RA and PsA patients capillaries showed venous limb diameter of 22 micron ± 4 and 18 micron ± 5 ($p<0,001$) respectively and arterial limb diameter of 16 micron ± 4 and 15 micron ± 3 ($p<0,05$) respectively. The average diameter of RA patients capillary loop was 30 micron ± 8 while was 27 micron ± 7 ($p<0,001$) in PsA patients. We found statistically significant differences in measures of the width of the capillary loop and of the linear density of capillaries. This study indicates that is possible to demonstrate, through the analysis of capillaroscopic images, significant differences in microcirculation between PsA and RA. These specific characteristics may be the basis of pathogenetic differences and provide additional information for correct differential diagnosis.

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LIFE THREATENING PUSTULAR PSORIASIS AS A RESULT OF STEROID WITHDRAWAL IN SERO-NEGATIVE ARTHRITIS: STEROID TACHYPHYLAXIS IS IT JUST A MYTH?

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A 60-year-old retired nurse with sero-negative arthritis was hospitalised with a 3 week history of progressive rash. Her oral medications had been altered significantly with a reducing prednisolone dose after the introduction of methotrexate, hydroxychloroquine and sulphasalazine over the previous 3 months; she had stopped these herself 2 weeks earlier.
On admission her rash was felt to be medication related but rapidly progressed necessitating urgent dermatology review. At this stage she was systemically unwell and erythrodermic with sheets of (sterile) pustules on a background of well demarcated scaly erythematous plaques accentuated over the extensor surfaces. A differential diagnosis of drug related acute generalised exanthematous pustulosis (AGEP) was considered but with the history of steroid withdrawal, a tachyphylactic pustular psoriasis was felt most likely. Histology was psoriasiform and cyclosporin (3mg/kg) was initiated. A rapid clinical response was seen within 3 days. Subsequently the cyclosporin was tapered and her arthritis controlled with anti-TNF therapy.
Steroid tachyphylaxis and pustular psoriatic flares as a result of their use topically or systemically for joint disease and respiratory disease was reported in the 1970s. As a result dermatologists tend to avoid unopposed topical steroids in psoriasis. However no true causal link has been confirmed. Awareness of this potential phenomenon beyond dermatologists is important due to significant associated morbidity and mortality usually as a result of its hemodynamic, thermodynamic and secondary infective consequences in the medically frail. Recognising that both AGEP and pustular psoriasis have no infective origin avoids inappropriate antibiotic treatment and hastens diagnosis.

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VITAMIN D LEVELS IN PATIENTS WITH PSORIASIS WITH OR WITHOUT ARTHRITIS

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Introduction: The immunomodulatory role of vitamin D might be particularly important in psoriasis (Ps) where sun or UV exposure may be used therapeutically.
Objective: to measure vitamin D and Parathyroid Hormone (PTH) serum levels in patients with psoriatic disease and the associations with some relevant clinical parameters.
Methods: Cross-sectional study on 126 consecutive patients (47 women, 79 men; mean age 52 years ± 14, range 18-88) affected by Psoriasis (Ps), not on vitamin D supplements or UV-B treatment, from 2 dermatology centres of northern and central Italy. Exposure to sunlight was quantified as minutes of exposure from March to September.
Results: the prevalence of Ps patients with vitamin D insufficiency (25OHD level <20 ng/ml) was 55% but this proportion rose to 85% on late winter. 25OHD levels were negatively correlated with serum PTH ($p=0.002$) but not with the skin involvement as assessed by Psoriasis Area and Severity Index.
Forty-five % of the patients had also overt arthritis (PsA). Slightly lower 25OHD levels were found in these patients as compared with patients with Ps only. This difference was borderline significant ($p=0.05$) when the data were adjusted for sun exposure and age: 25OHD 22.0±1.6 (S.E.) vs. 18.4 ±1.7 ng/ml, in Ps and PsA, respectively.
Conclusions: The prevalence of vitamin D insufficiency in Ps patients is very high particularly during late winter and early spring. Vitamin D deficiency is apparently more frequent in patients with PsA.

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PRECLINICAL ENDOTHELIAL DYSFUNCTION IN PSORIATIC ARTHRITIS

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Background: Psoriatic arthritis (PsA) is defined as an inflammatory arthritis associated with psoriasis. Increased common carotid intima-media thickness (IMT) has been previously demonstrated in PsA as a marker of subclinical atherosclerosis. Moreover, PsA duration has been found positively association with the development of enhanced atherosclerosis. The aim of this study was to investigate coronary microcirculation and endothelial function in PsA at the onset of the disease.
Methods: Twenty-five patients with new diagnosis of PsA (12 F and 13 M; mean age 55±10 years) without clinical evidence of coronary artery diseases and 20 healthy controls underwent dipyridamole echostress with coronary flow reserve (CFR) evaluation, plasma asymmetric dymethilarginine (ADMA) levels determination by high performance liquid chromatography and ultrasound evaluation of common carotid IMT.
Results: PsA patients had reduced CFR (2.77±0.70 vs 3.5±0.8; $p<0.001$) and increased plasma ADMA levels (0.68±0.07 vs 0.52±0.2; $p<0.001$) compared to healthy controls. Common carotid IMT did not differ between the 2 groups. Among PsA patients, we found a negative correlation between CFR and age ($p=0.002$) and between CFR and plasma ADMA levels ($p=0.002$). In addition, we found CFR was positively related to deceleration time ($p=0.05$) and E/e' of the interventricular septum ($p=0.02$). Plasma ADMA levels were negatively correlated to E/e' of the interventricular septum (P=0.02). Common carotid IMT did not differ between the 2 groups.
Conclusion: PsA is early associated with preclinical endothelial dysfunction and impaired coronary microcirculation despite normal common carotid IMT in absence of signs and symptoms of CV involvement and traditional CV risk factors.

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THE SIGNIFICANCE THE ROLE OF ANTI-TNF-ALPHA EFFECTS ON ENDOTHELIAL DYSFUNCTION IN PSORIASIC ARTHRITIS

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The high incidence of cardiovascular disease in psoriatic arthritis (PsA) is referred, to the direct action of TNF-α and other inflammatory cytokines on the endothelial cells, resulting in a reduced NO bioavailability with endothelial dysfunction and subsequent cardiovascular events, potentially counteracted by the anti-TNF-α drugs.This study aimed to evaluate by high-resolution ultrasound of the brachial artery the endothelium-dependent, flow-mediated dilatation (FMD) and the endothelium-independent, nitroglycerin-mediated dilatation (NMD), in eleven patients (5 females and 6 males, aged 46.6±12.4 years), with PsAr, treated with etanercept (4 cases) or adalimumab (7 pts). The patients showed an impaired FMD respect to controls (5.9±3.1 vs 13.4±5.45 $p<0.01$), with abnormal baseline values in 4 cases (2 etanercept and 2 adalimumab pts) and lower NMD than controls (13.9±5.6 vs 19.2±4.2, $p<0.05$).The anti-TNFa treatment improved the FMD at 1 year (9.9±4.5 vs. 5.9±3.1 $p<0.05$) and at 2 years of treatment (2.11±5.7 vs. 5.9±3.1 $p<0.05$), regardless of the TNF antagonist agent used. Our results demonstrate the high prevalence of ED in PsA, as a marker of vascular activation with functional alterations, potentially reversible; in particular, a normalized endothelial function anticipates and accompanies the overall clinical response to treatment, and conversely the persistence or the recurrence of a reduced FMD appears to increase the likelihood of a loss of response to drug or adverse cardiovascular events,both occurring in subjects with endothelial dysfunction at baseline.

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BONE MARROW LESIONS BY MRI IN PATIENTS WITH EARLY HODGKIN´S LYMPHOMA MAY MIMIC INFLAMMATORY LESIONS SIMILAR TO PATIENTS WITH SPONDYLOARTHRITIS

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Background: A member of other pathological conditions may mimic the inflammatory lesions seen in spondyloarthritis (SpA). It is important to realize that inflammation of sacroiliac joints (SIJ) and spine in patients (pts) with SpA attributable to clinical manifestation.
Objective: To describe the rather like SpA MRI lesions and clinical manifestation in 2 pts with very early stage Hodgkin´s lymphoma.
Study patients: 2 consecutive pts 20 and 27 old with low back pain more 3 month complained of night pain in buttock and lumbar, incidence onset of pains, low grade fever and increased CRP and ESR. Both were HLA B27 (-). MRI (1,5 Tesla, T1, T2-FS, 4mm) of the SIJ (both) and lumbar spine (1 pt) was conducted in semi coronal (SIJ) and sagittal (LS) planes. One of them has fever incident for 3 days in 2 month past history that diagnosed as acute respiratory disease. One of them had alone small-size neck node (0.5x0.5sm). Other patient hadn't any lymph nodes in the direct palpation of the neck and axillary space.
Results: Substantial MRI's bone marrow edema was detected in bone iliac, sacrum and lumbar spine (Fig. 1, 2.). The pts were referred to ultrasound of neck and thoracic cavity and visualized multiple lymph nodes. Hodgkin's lymphoma diagnosis was confirmed by lymph nodes biopsy and they had started the treatment in Haemotological Centre.
Conclusion: Night low back pain and MRI's bone marrow edema can be detected in young patients with early stage of HL.

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FEVER OF UNKNOWN ORIGIN AS ONSET IN SERONEGATIVE SPONDYLOARTHROPATHIES

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The seronegative spondyloarthropathies are chronic inflammatory disorders characterized by articular manifestations and extra-articular symptoms. However in some cases, they may begin in an atypical way, only with fever of unknown origin (FUO).
We describe three patients which began with fever and then the final diagnosis was psoriatic arthritis in the first two patients and ankylosing spondylitis in the third one. In all these cases fever disappeared after treatment with anti-TNF drugs.

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ANTERIOR UVEITIS DEVELOPMENT IN ANTI-TNF TREATMENT USING PATIENTS WITH ANKYLOSING SPONDYLITIS

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Aim: Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by axial involvement and enthesitis. One of the most important extra-axial involvement is the development of anterior uveitis. The role of anti-TNF agents in the development of anterior uveitis is controversial. In this study we aimed to investigate the frequency of uveitis development in AS patients using anti-TNF treatment.
Methods: The study group consisted of 123 AS patients using anti-TNF treatment (93 male, 30 female; median age:35 (20-68); median disease duration: 5 years (1-33)). All patients fulfilled Modified New York Criteria for AS. All patients were examinated for uveitis.
Results: 64.3% of the patients were using infliximab, 28.5% etanercept and 30.9% adalimumab. 14 patients (11.4%) had a history of uveitis before anti-TNF therapy and 9 patients (7.3%) had after anti-TNF treatment. Only in 1 of 14 patients with a history of uveitis before anti-TNF treatment, uveitis repeated during treatment with infliximab. The other 8 patients with after the TNF treatment developing uveitis had no history of uveitis previously. Uveitis during etanercept therapy was seen in 2 patients; during infliximab treatment in 6 patients. There is no significant difference between infliximab,etanercept and adalimumab for the development of uveitis (p=0.094). During the infliximab therapy the frequency of uveitis was relatively increased.
Conclusion: Uveitis may be seen during the treatment with anti-TNF agents. The frequency of the development of the uveitis under the anti-TNF therapy is not statistically different with different anti-TNF agents.

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DISTRIBUTION OF HLA-B27 AND ITS ALLELES IN PATIENTS WITH ANKYLOSING SPONDYLITIS IN MOROCCO

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Ankylosing spondylitis or AS, is a form of arthritis that primarily affects the spine, although other joints can become involved. Even if the exact cause of AS is unknown, we do know that genetics play a key role in AS. Most individuals who have AS also have a gene that produces a "genetic marker" - in this case, a gene called HLA-B27. The purpose of the present study was to investigate the frequency of HLA-B27 and its alleles in ankylosing spondylitis in Moroccan patients. HLA-B27 alleles were typed by PCR amplification with sequence-specic primers. We studied 55 patients with ankylosing spondylitis, 16 were HLA-B27-positive (29%) and we also studied 144 healthy controls. There was an increased frequencies of HLA-B27 (X^2=69.44, $p<0.001$, OR= 38.97). Four B27 subtypes were identified: B*2702, 03, 05 and B*2708. The distribution of these alleles in the AS patients was 25% for B*2702, 12.5% for B*2703, 56.25% for B* 2505 (RR=7), and 6.25 % for B*2708. To sum up we can say that a RR of 7 between HLA-B2705 and AS is statistically highly significative.

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RISK FACTORS ANALYSIS FOR INFECTIONS IN 174 PATIENTS WITH SPONDYLOARTHRITIS: A SINGLE CENTRE

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Introduction: The development of infections is the most frequent adverse event during the therapy with anti-TNF-α inhibitors.
Objective: To analyse the frequency of infectious events (IE) and the risk factors in patients affected with Spondyloarthritis (SpA) treated with anti-TNF-α inhibitors.
Materials and methods: 174 patients (males 70,7%) were evaluated at the Outpatient Unit Rheumatology of Padua from 2004 till 2009.54 (31%) received infliximab (I) 3 mg/kg every 6-8 weeks, 76 (43,6%) etanercept (E) 25 mg twice a week and 44 (25,4%) adalimumab (A) 40 mg fortnightly, 53 (30%) received also DMARDS, only 3 (2%) corticosteroids. We considered disease duration, therapy duration, age, sex, disease activity (BASDAI), comorbidities, association with DMARDS and steroids therapy as possible risk factors for IE. We divided the patients in two

groups: who developed one or more IE and patients without. Chi-square test was performed for statistical analysis.
Results: The mean age was 47 years old (± 11,1), the disease duration 11,7 years (± 8,3), the mean therapy duration with inhibitors of TNF-α 31,2 months (± 16,4). 48 patients (27,5%) presented comorbidities. 17 patients (9,7%) developed IE, 9 (52,9%) were afflicted by other affections (comorbidities or protesis). 157 patients did not develop IE, of these 24,8% presented risk factors for IE. A significant statistical difference was found between the two groups performing the chi-Square test (X2=6,06, *p*=0,01).
Conclusions: Comorbidities represent the major risk factor for developing IE, whereas the other parameters do not seem to influence the safety of TNF-α inhibitor.

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FUNCTIONAL POLYMORPHISMS OF PTPN22 AND APO-1/FAS GENES IN TUNISIAN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Ankylosing spondylitis (AS) is a common inflammatory arthritis characterized by axial skeletal inflammation, enthesitis, and association with HLA-B27. Cytokines, and counter-regulatory molecules play important roles in the regulation of inflammatory response, and seem to be good candidates involved in the development of this pathology. The objective of this study was to access the influence of single nucleotide polymorphisms (SNPs) 620 R/W and -670 G/A of protein tyrosine phosphatase non receptor type 22 and Apo1/Fas, respectively, on AS susceptibility and prognosis. SNPs were determined by restriction fragment length polymorphisms in 90 AS Tunisian patients and 100 ethnic-matched healthy subjects. No significant skewing of Apo-1/Fas polymorphism was seen in AS group. However, we found strong evidence of an association of PTPN22 620W allele and AS (*p*=0.00009, OR: 11, 95% CIs, [2.51-7.48]). In addition, this W variant allele was associated with hip involvements in AS patients (*p*=0.023, OR: 3.05, 95% CIs, [1.12-8.32]). Nevertheless, analysis does not detect an association between the age at onset, the presence of extra-articular involvement, severe limited spinal mobility or radiological damage and PTPN22 W allele.
In conclusion, we have demonstrated that PTPN22 620W allele is associated with Tunisian AS susceptibility and could have a small influence on AS prognosis. A large number of samples are required to provide independent confirmation of these findings.

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LEPTIN SERUM LEVEL IN DIFFERENT SUBTYPE OF MULTIPLE SCLEROSIS, CAN LEPTIN LEVELS PREDICT THE PROGRESSION OF MULTIPLE SCLEROSIS?

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Background: Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) resulting in accumulating neurological disability. Recent evidences have strongly indicated that leptin , an adipocyte-secreted hormone/cytokine belonging to the helical cytokine family, has some influences on the immune system and maybe involved in the pathogenesis of autoimmune diseases such as MS.
Objectives: To study the serum levels of leptin among patients with different subtypes of MS and to shed light on its association with disease progression.
Material and methods: We measured and compared leptin concentrations in sera of 136 patients with different types of MS, including 93 relapsing remitting (RR), 18 primary progressive (PP), 13 secondary progressive (SP), and 12 progressive relapsing (PR) after matching for sex, age and BMI using an ELISA technique.
Results: Statistically significant difference was observed between SPMS and PPMS (24.18±21.9 ng/ml vs 70.27±52.55 ng/ml, $p<0.01$), and also between RRMS and PPMS (42.10±42.35 ng/ml vs 70.27±52.55 ng/ml, $p<0.05$). There was a tight correlation between Progression Index (EDSS/disease duration) and leptin serum concentration (F=21.7, $p<0.001$). Furthermore some degree of significantly differences was seen in sex and BMI factors between groups.
Conclusion: Leptin serum level is significantly higher in the sera of patients with progressive forms and also seem to be associated with disease progression.Our data suggests a pro-inflammatory role for leptin in MS as a model of autoimmune disease.

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DYSFUNCTION OF SELECTIVE SUPPRESSION OF AUTO-ANTIBODY PRODUCTION IN SLE MICE AND RECONSTRUCTION OF THIS MECHANISM BY INDUCTION OF BONE-MARROW CHIMERISM

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Background: Mixed chimerism induced by hematopoietic stem cell transplantation is useful in the treatment of autoimmune diseases, but the detailes of the mechanism by which mixed chimerism reverses the autoimmune state have not been determined. Here, we propose a potential mechanism in which newly developed T cells positively selected by the recipient's thymus are able to regulate autoreactive B cells. To test this hypothesise, we investigated whether MHC/TCR cognate interaction was important for the regulation of autoreactive B cells. We induced an auto-cross-reactive antibody (Ab) by immunizing foreign antigen with a homolog to an auto-antigen in a BXSB lupus mouse strain achieving MHC-matched or fully-mismatched mixed chimerism.
Methods: Male BXSB mice (H-2^b) received BM cells from C57BL/6 (H-2^b), B10D2 (H-2^d) or F1 mice (H-$2^{b/d}$) with non-lymphoablative conditioning. Stable multi-lineage mixed chimerism was established as previously reported. Normal control mice, BXSB, and chimeric mice were immunized with 100μg pigeon cytochrome C (PCC) emulsified in CFA (i.p.), then weekly immunized for seven weeks with 100μg PCC. Anti-PCC and anti-mouse cytochrome C (MCC: cross-reactive with PCC) antibody were analyzed through ELISA.
Results: In normal mice and MHC-matched/haploidentical chimeric mice, the titer of anti-MCC Ab plateaued at low levels. In BXSB and fully MHC-mismatched chimeric mice, however, anti-PCC/MCC Ab rose higher. These results suggested that the regulatory mechanism selectively suppresses auto-reactive antibody production through cognate interaction. Dysfunction of this suppression system is one possible cause of lupus; the induction of BM mixed chimerism may allow us to the reconstruct the system, however.

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PLEUROPULMONARY MANIFESTATIONS OF CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS; A DESCRIPTIVE STUDY OF 18 PATIENTS

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Objective: Childhood-onset systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease that can involve multiple organs such as: skin, kidney, musculoskeletal system, brain, and others as well as lungs. Although pulmonary involvement is relatively frequent in adult patients, it has rarely been reported in children with SLE. Pulmonary manifestations may be an initial and life-threatening complication of SLE in children. The aim of this report is to describe pleuropulmonary manifestations of childhood -onset SLE via description of our patients.
Methods: We retrospectively studied medical records of children with childhood-onset or JSLE, admitted to Children's Medical Center from 1995 to 2005. These records were evaluated for evidence of pleuropulmonary involvement. All patients fulfilled at least four of the classification criteria of the American Rheumatism Association.
We obtained data regarding the age, sex and clinical and laboratory features. Informed consent was obtained from all patients.
Results: Overall, our study concerned sixty-four patients. Fifty-five of these patients (86%) were female and 9 patients (14%) were male. Eighteen of the 64 cases (28%) had pulmonary involvement. Among these 18 patients, pulmonary complications included: pleuritis in 33.3%, acute lupus pneumonitis in 11%, chronic interstitial pneumonitis (CIP) in 5%, infectious pneumonia in 33.3%, pulmonary vasculitis in 5%, and pulmonary embolism in 5%.
Conclusion: The pleuropulmonary manifestations of childhood-onset SLE range from the minor pleuritic pain caused by serositis to life-threatening consequences of pulmonary hemorrhage.

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MACROPHAGE ACTIVATION SYNDROME IN CHILDREN WITH RHEUMATIC DISORDERS: A 5 CASE SERIES

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Background: Macrophage activation syndrome (MAS) is a rare complication of childhood with rheumatic disease. This syndrome has been reported as a complication of many rheumatic diseases, most commonly in systemic onset of juvenile idiopathic arthritis (SoJIA). The aim of this study was evaluation the rate, symptoms and outcome of MAS in a Pediatric Rheumatology Department of Children's Medical Center during 10 years.
Methods: Retrospective review of cases of MAS from the charts of 120 patients with juvenile rheumatoid arthritis and systemic lupus erythematosus (SLE), were reviewed collected data base of 5 children with MAS from 1998 to 2007, in Pediatric Rheumatology Department of Children's Medical ,In Tehran University.
Results: Totally 120 patients evaluated in this study including 108 JIA and 12 SLE. Five patients (four girls), and (one boy) were considered to have evidence of MAS. The incidence of MAS in our study was 4.2%. This rate for all JIA patients was 3.7%. Mean age of MAS onset was 4.9 years, and duration of rheumatologic disease prior to MAS, 22 months. Four cases (80%) had abnormal liver function during the disease course, and coagulopathy. Bone marrow examination supported the diagnosis with definite haemophagocytosis in four cases (80%). The mortality rate was 40%.
Conclusion: Although MAS is a rare complication of rheumatologic disorders, because it is potentially fatal it must be thought in each childhood rheumatic disorders with suddenly changes in general condition and decrease peripheral cells.

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INDIVIDUAL BASED VACCINATION APPROACH: WHY NOT? IMMUNE SYSTEMS ARE NOT IDENTICAL AND VARIES WITH AGE AND SINGLE PERSONS

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Background: Italian Constitution does not allow any medical intervention without consent of the patient (except for psychiatric or drug addicted patients) and guarantees freedom in treatments choice. The National Vaccinations Plan defined compulsory vaccines as an ancient concept to overcome.
Objective: Evaluate the rationale of a lifelong individual-based vaccination approach.
Methods: We reviewed official epidemiological data about incidence and vaccine coverage of major preventable diseases.
Results: 15 million Italians are unprotected against diphtheria but the last case has been reported in´91. There were 74 tetanus cases in 1999-2004 (no paediatric cases since'93) with men 65-69 and women 80-84 representing most of those: having vaccine a short duration, wounds and tissue oxygenation are crucial. Hepatitis B vaccine is compulsory only in Italy for newborns despite 15years proved efficacy and presenting the highest failure rate if run <1 year of age. As there are 1000 hepatitis B cases yearly >24 years old, sexually active ages should be mostly treated. There were 0.85/100,000 pertussis cases <1 year of age in 2003, being the new vaccine only 88% effective with serious side effects: does long-term breastfeeding may be protective? We are aware that Salk vaccine offered in polio free countries is not so protective against wild virus still infecting India and Guinea gulf, and that its duration is still unknown.
Conclusion: Combined vaccines may reduce people's freedom of choice and cause safety questions. Given the current vaccination coverage and incidence data, a lifelong individual-based vaccination approach could be an acceptable strategy for the prevention of infectious diseases.

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IS AUTOIMMUNITY A SIGN OF OUR TIMES? STRESS, LUPUS, AND LATE CAPITALISM

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Autoimmune disorders, such as lupus, take shape in the interaction between genes and environment. Though viruses and industrial pollutants are typically identified as potential environmental culprits behind lupus, a growing body of research emphasizes the effect of stress on autoimmunity. Drawing upon etymological data, this paper situates stress as a newly emergent, harmful by-product of the current late capitalist "socioeconomic environment"; it is posited that rising rates of lupus and autoimmunity reflect the present condition of this stratum of the environment. Prominent works from the field of anthropology - which forefront the closely intertwining relationship between the body and society, culture, and the economy - are revisited in favor of this argument, and the reality of the socioeconomic environment is underscored.

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PREVALENCE OF C-REACTIVE PROTEIN ELEVATION AND TIME COURSE OF NORMALIZATION IN ACUTE PERICARDITIS: IMPLICATION FOR THE DIAGNOSIS, THERAPY AND PROGNOSIS

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Background: Aim of this study is to prospectively evaluate the frequency of high sensitivity C-reactive protein (hs-CRP) elevation in patients with acute pericarditis, its time course of normalization.
Methods and results: Two hundred consecutive patients with viral or idiopathic acute pericarditis (mean age 53±15.5 years, 103 males) were studied from August 2005 to August 2007 in two Italian referral centres. Hs-CRP was determined at presentation and then every week till normalization. Hs-CRP was elevated in 156 of 200 cases (78%) at presentation. Causes of a negative hs-CRP at presentation were: early assessment in 15 of 44 cases (34%) becouse hs-CRP became positive at a second determination within 1 week, and previous anti-inflammatory therapies in 22 of 44 cases (50%). Hs-CRP normalization was achieved with the following time course: 120 of 200 (60%) at week 1, 170 of 200 (85%) at week 2, 190 of 200 (95%) at week 3, all cases (100%) at week 4. In multivariable analysis, incomplete response to empiric anti-inflammatory therapy at week 1 (HR 2.98 95%CI 1.80-4.94; $p<0.001$), corticosteroid therapy (HR 2.80 95%CI 1.59-4.95; $p<0.001$), and the presence of elevated hs-CRP at week 1 (HR 2.36 95%CI 1.32-4.21; $p=0.004$) were independent risk factors for recurrences. So only 7 of 200 patients (3.5%) had a persistently normal hs-CRP with no previous treatment.
Conclusions: Hs-CRP is elevated at the initial presentation in about 3 of 4 cases of acute pericarditis, identifies patients at higher risk of recurrences, could be used to monitor disease activity and select appropriate therapy length.

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SERUM IMMUNOGLOBULIN LEVELS AND CYTOKINE CONCENTRATIONS IN CHILDREN WITH CHRONIC TONSILLITIS BEFORE AND AFTER TONSILLECTOMY: A FOLLOW UP STUDY

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Background: Recurrent tonsillitis mainly affect children and it is the most common cause of primary care visit to physicians and tonsillectomy is one of the most frequently performed surgical procedure on children. Nevertheless, the ultimate effect of chronic tonsillitis and the procedure of tonsillectomy on the immune system are still uncertain.
Aim: evaluate changes in serum immunoglobulin levels and cytokines IL-6, INF gamma (INF-γ) concentrations in children with chronic tonsillitis 24 hours before and 3 months post tonsillectomy and the effect of tonsillectomy.
Patients and methods: The study was conducted on 20 children with chronic tonsillitis their mean age were (8.30±2.59) years and 10 healthy). 24 hours prior tonsillectomy and 3 months post tonsillectomy serum immunoglobulin's (IgG, IgM, IgA) and cytokines (IL-6 and INF-γ) serum concentrations were measured.
Results: Children with chronic tonsillitis24 hours before tonsillectomy showed high levels of IgG, significant high levels of IgM, and significant low levels of IgA

compared to control group . Also there were Significant high levels of IL-6 and INF-γ. There was no significant difference in immunoglobulin levels (IgG, IgM, IgA) prior to and 3 months post tonsillectomy. Significant low levels of IL-6 and INF-γ 3 months post tonsillectomy .
Conclusion: Children with chronic tonsillitis had a lower levels of IgA, tonsillectomy do not compromise the humoral immune function in children ,while significant reduction in elevated levels of IL-6 and interferon-g suggested that it have a role in chronic tonsillitis and this finding is important for the immunologic aspect of the disease.

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A CLINICAL STUDY ON GLUCOSAMINE SULFATE VERSUS COMBINATION OF GLUCOSAMINE SULFATE AND NSAIDS IN MILD TO MODERATE KNEE OSTEOARTHRITIS

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Osteoarthritis (OA) is the most common form of arthritis. In patients with mild to moderate osteoarthritis, apart from the existing approved medicinal oral drugs (paracetamol and NSAIDs), physical exercise is the only alternative to obtain symptomatic relief. Currently, arthroplasty is the only curative or disease-modifying treatment that exists. Glucosamine was mainly introduced on the world-wide market as a food-supplement but with the aim to improve symptoms in patients with OA or joint pain or function. This study was aimed to assess and ensure the safety, therapeutic efficacy and improvement in joint physical function of mild to moderate knee OA patients treated with Glucosamine Sulfate (GS) - Group A, compared with a combination of GS and NSAID - Group B. The study involved 82 mild to moderate knee OA patients from South Indian population with the mean age of 50.81±6.335, who were administered the therapy for 3 months. It was observed that even though the Group B patients showed definite improvement in the WOMAC index of OA questionnaires and visual analogue scale pain score, the Group A patients too showed remarkable improvement in joint pain, stiffness and physical function with minimal side effects. Thus it can be concluded that rather than depending on the combination of GS with NSAIDs, the GS alone therapy would be sufficient to improve the quality of life of mild to moderate knee OA patients with the added advantage of lessening the side effects.

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IS STEROID PULSE THERAPY WARRANTED IN PATIENTS WITH KAWASAKI'S DISEASE WHO SHOW AN INITIAL INADEQUATE RESPONSE TO GAMMAGLOBULIN TREATMENT?

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Introduction: Current first-line treatment of Kawasaki's disease is administration of intravenous gammaglobulin (IVIg). However, 15-20% of patients demonstrate an inadequate initial response. The use of pulsed steroid therapy (IVMP) may be warranted in these patients.
Methods: PubMed- searched with MeSH terms "Kawaski" and "Methylprednisolone", Secondary sources- British National Formulary for Children 2010-2011 The literature was analysed to determine whether pulsed steroid therapy is warranted and cost-effective in treatment of Kawasaki's disease in patients who fail to respond initially to IVIg. Outcomes assessed included inflammatory markers, duration of fever, complications and cost of therapy.
Results: In the treatment of IVIg-resistant Kawasaki's disease, IVMP has been shown to be at least as efficacious as continued IVIg therapy. The largest study even reported a significant reduction in duration of fever when treated with IVMP compared to IVIg. The average duration of fever being 1±1.3 days, and 3±2.4 days, respectively ($p<0.05$). No major or permanent side effects have been reported with IVMP therapy in a wide range of studies. In terms of cost, at just £3.20 per kilogram of bodyweight, IVMP is far cheaper than IVIg which at the lowest price is £76.00 per kilogram of bodyweight.
Conclusion: IVMP appears to mitigate disease faster than continuing IVIg. It is also safe. As IVMP is cheaper than continued IVIG, it may be the preferable treatment option. Further evaluation through cost analysis and double-blinded randomized control trials is required to fully determine efficacy and economical benefits.

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ADALIMUMAB AND POLYMYALGIA RHEUMATICA. CLINICAL REMISSION BUT PERSISTING HIGH LEVELS OF ESR: A CONTROVERSY

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Objective: We aimed to test Adalimumab, a fully humanized monoclonal antibody directed toward TNF in Polymyalgia Rheumatica (PMR) refractory to glucocorticoids (GC) and immunosuppressive treatments.
Methods: Adalimumab 40 mg was administered subcutaneously every two weeks in two patients with relapsing PMR resistant to immunosuppressive agents who were not able to reduce methylprednisolone below 16 mg/day besides severe GC-induced side effects (diabetes, osteoporosis, hypertension). The patients were regularly monitored for clinical symptoms, glycaemia, erythrocyte sedimentation rate, C-reactive protein levels and arterial blood pressure during a fifteen months follow-up.
Results: Both patients had clinical improvement in morning stiffness at the shoulder and pelvic girdle, neck and hands arthritis. In both patients steroid therapy was tapered to suspension. Glycaemia and blood pressure values normalized, and the anti-diabetic and anti-hypertensive agents were also suspended. Interestingly, in both patients, while CRP levels turned into normal values, ESR levels remained elevated during all the follow-up period.
Conclusions: Our results suggest that Adalimumab may be a safe and effective treatment for PMR to be used as a steroid-sparing agent in selected patients.

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TOCILIZUMAB IN THE TREATMENT OF ARTHRITIS: RESPONSE TO THERAPY AND EVALUATION OF B CELLS SUBSETS AFTER 4 MONTHS TREATMENT

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Background: IL-6 has pleiotropics effects on immune system cells; in rheumatoid arthritis, it is responsible for ESR and CRP elevation, articular damage and clinical activity. Blocking IL-6 receptor with Tocilizumab leads to clinical improvement of arthritis and seems to reduce peripheral pre- and post-switch memory B cells in rheumatoid arthritis.To evaluate B cells subsets distribution and their relation to clinical improvement after Tocilizumab therapy.
Methods: 5 patients (3 RA, 1 JRA and 1 AOSD) were treated with monthly 8 mg/kg intravenous tocilizumab. Peripheral B subset distribution was evaluated with flow-cytometry (IgD-CD27) at baseline and after 4 months of treatment. Clinical data was collected and disease activity was assessed using DAS over time.
Results: A significant reduction of ESR and CRP was observed after 4 months therapy (ESR: 41.0±27.9 vs 8.4±7.9mm/1st hr, p=0.01; CRP:51.3±86.6 vs 1.7±1.7 mg/l, p=0.01) even if DAS reduction didn't reach statistical significance (3.5±0.4 vs 2.1±1.6, p=0.09) due to a limited reduction of swollen and tender joints count (SJC:5.8±5.0 vs 2.6±3.6, p=0.31; TJC:10.0±10.8 vs 8.0±6.4, p=0.84).Considering B cells subsets, we observed a trend to a decrease of percentage of pre-switch memory B cells (IgD+CD27+: 26.9±22.9% at baseline vs 14.2±15.3% at 4th month FU, p=0.22) and an increase of frequency of naïve B-cells (IgD+CD27-: 36.6±21.2% vs 57.7±14.9%, p=0.15) after treatment. A parallel decreased of CD19+/ZAP70+ during FU was observed (8.9±5.5% vs 2.7±2.0%, p=0.19). Memory B cells (CD27+IgD-) weren't modified by treatment.
Conclusions: Tocilizumab rapidly reduce inflammation and even in a short term follow-up seems to alter the peripheral B cells phenotype.

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ANTI-TNF THERAPY INDUCES CHANGES ON T CELLS AND NK CELLS SUB-POPULATIONS IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Although the role of TNF in late steps of rheumatoid arthritis (RA) inflammatory cascade is fairly well-known, its influence over earlier pathways is less understood. The aim of this study was to evaluate the effect of adalimumab on RA patients' lymphocyte subsets, and correlate their changes with clinical response.
Methods: Eighteen RA patients received adalimumab during 24 weeks and responsiveness to treatment was evaluated with ACR20 criteria. Peripheral blood Th1, Th17 and T regulatory cells (Tregs) subpopulations, CD8+ T cells, NK and B cells were assessed by flow cytometry at the beginning and at the end of the study.
Results: Th1 cells were decreased by anti-TNF therapy, unrelated to the clinical response. Th17 cells were also decreased, but only on non-responder patients. Conversely, the proportion of Tregs was increased at 6 months, as was the percentage of IFN-gamma-secreting NK cells. Before anti-TNF administration, the proportion of Th17 cells was directly correlated with Th1 cells, but inversely correlated with IFN-gamma-secreting NK cells; these correlations were lost after therapy.
Conclusions: Adalimumab was able to modulate the proportion of Th1 and Th17 cells, both of them involved in RA pathogenesis. Simultaneously, an increase in Tregs and in IFN-gamma-secreting NK cells was observed. We postulate that local rise in IFN-gamma production due to recovery of NK cells' function secondary to TNF blockade, together with Tregs, lead to an inhibition of Th17 differentiation in an inflammatory context, although these immunological changes do not always translate into clinical recovery.
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ANTI-TNF-A MODULATE THE PRODUCTION OF TH1 CYTOKINE AND NITRIC OXIDE IN PATIENTS WITH BEHÇET DISEASE

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Behçet's disease (BD) is a chronic inflammatory multisystemic disorder with unknown aetiology. BD is associated with Th1/Th2 cytokines dysregulation and neutrophiles hyperactivation. We investigated here Th1 cytokines and nitric oxide production in different types of manifestations of BD. We evaluated the effect of anti-TNF-α treatment on IL12 and NO induction in PBMC from Algerian patients with BD. cells of patients spontaneously secreted IL12 and NO in all types of manifestations of BD. Phytohaemaggultinine (PHA) stimulation induced production of large amounts of IL12 and NO. Next, we monitor cytokines and NO production during short-time of treatment with anti-TNFα antibody. The effect of anti-TNF-α significantly reduced the number of PBMC secreting IL12 ($p<0.05$). A rise in IL12 production was associated with clinical manifestations. In contrast, anti-TNF-α treatment induced a significant decrease in the production of nitric oxide in all type of manifestation ($p<0.01$). Taken together our findings indicate that TNF-α plays a pivotal role in BD and treatment with anti-TNF-α may have important implications for the treatment of BD.

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B LYMPHOCYTE DEPLETION THERAPY WITH RITUXIMAB IN CHILDREN WITH REFRACTORY SYSTEMIC LUPUS ERYTHEMATOSUS NEPHRITIS

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Objective: To determine the safety and efficacy of B lymphocyte depletion therapy in patients with refractory childhood -onset systemic lupus erythematosus (SLE) with lupus nephritis.
Methods: Seven patients (5 female), and (2 male) ages 5.7-15.4 years (median 12.8 years) with active SLE that was resistant to standard immunosuppressive agents were treated with B cell depletion refractory to classic treatment.During a 2-week period, patients received high-dose oral corticosteroids, and intravenous cyclophosphamide, and 750-mg/m^2 intravenous infusions of rituximab**.**
Results: In all patients, the clinical symptoms and signs for which rituximab therapy was initiated were improved. There was significant improvement in the Lupus Assessment Group global scores. In 2 patients have subsequently shown further significant improvement in renal function and proteinuria. Patients were followed up for a median of 1.0 years, and no serious adverse effects were noted.
Conclusion: This study demonstrates that targeted B cell depletion therapy can be a safe and efficacious addition to therapy with standard immunosuppressive agents in patients with refractory childhood SLE. The drugs used for treatment of childhood SLE need to be the most effective, least toxic agents, allowing normal growth and development.

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BENEFICIAL EFFECT OF JEECHOOL-WHAN IN ALLERGIC RHINITIS

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Jeechool-Whan (JCW) is traditional Korean medicine. It has been used treatment of the allergic disorders. JCW consists of *Atractylodes macrocephala* Koidzumi and *Ponciri Fructus* herbs. Imperatorin (IPT) is a component of the *Atractylodes macrocephala Koidzumi*. To investigate the effect mechanism of IPT in allergic rhinitis, the anti-allergic effect of IPT was analyzed by using in vivo and in vitro model. The number of nasal, ears, and eyes rubs after the ovalbumin (OVA) challenge in the OVA-sensitized mice was significantly higher than that in the OVA-unsensitized mice. Increased number of rubs was inhibited by administration of IPT. Increased levels of IgE in serum, spleen, and nasal mucosa of the OVA-sensitized mice were reduced by IPT administration. Histamine level was reduced by IPT-administration in serum of the OVA-sensitized mice. Protein levels of IL-1β, MIP-2, and ICAM-1 in nasal mucosa, IL-1β, IL-4, and IFN-γ in spleen tissue and mRNA expressions of IL-1β were inhibited by IPT-administration in the OVA-sensitized mice. In the IPT-administered mice, mast cells and eosinophils infiltration increased by OVA-sensitization were decreased. In addition, IPT inhibited the COX-2 protein expression and caspase-1 activity in same nasal mucosa tissue. In activated human mast cells, the IKK-b, RIP-2, NF-κB/Rel A and caspase-1 activation increased whereas IKK-b, RIP-2, NF-κB/Rel A and caspase-1 activation was inhibited by treatment of IPT. These results indicate that IPT ameliorate the allergic inflammatory reactions such as allergic rhinitis.

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ANTI-TNF-ALPHA THERAPY INDUCES INCREASE IN TRIGLYCERIDE LEVELS IN PSORIATIC ARTHRITIS PATIENTS

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Objectives: To evaluate lipid profile changes after anti-TNF therapy in patients with psoriatic arthritis (PsA).
Methods: Sixteen PsA patients (nine polyarticular, four oligoarticular, two axial and one mutilating) under anti-TNF (infliximab n=15 and etanercept n=1) were included. None had *dyslipoproteinemia or previous statin use. Total cholesterol (TC) and its fractions, inflammatory markers and prednisone use were evaluated.*
Results: The comparisons of lipid levels between baseline and after three months (3M) of anti-TNF therapy showed that there was a significant increase in mean triglycerides (117.8±49.7 vs. 140.1±64.1mg/dL, $p=0.028$) and VLDL-c (23.6±10.5 vs. 28.4±13.7mg/dL, $p=0.019$). In contrast, there were no differences in the mean TC ($p=0.28$), LDL-c ($p=0.42$) and HDL-c levels ($p=0.26$). Comparisons of the frequencies of altered lipid levels at baseline and at 3M were alike ($p>0.05$). Reinforcing, positive correlations were found between VLDL-c and CRP (r=0.647, $p=0.009$) and between triglycerides and CRP (r=0.604, $p=0.017$) levels at 3M. ESR reduction was observed after 3M ($p=0.04$). Mean prednisone dose remained stable at beginning and at 3M ($p=0.37$).
Conclusion: The negative effects of anti-TNF therapy on triglycerides levels suggest that more studies are necessary to clarify if these changes can reduce the beneficial effect of these drugs in cardiovascular morbidity in PsA patients.
Funding: This study was supported by FAPESP (Grant 2009/51897-5), CNPQ (Grants 305468/2006-5 to EB, 300248/2008-3 to CAAS and 300665/2009-1 to JFC) and the Federico Foundation Grant to EB, CAAS and JFC.

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ROLE OF TACROLIMUS IN THE TREATMENT OF LUPUS NEPHRITIS – A REVIEW OF EFFICACY AND CLINICAL EXPERIENCE

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Introduction and objective: Lupus nephritis is a serious complication of systemic lupus erythematosus(SLE) and is often a therapeutic challenge. Various immunosuppressants have been used for induction-remission and maintainence therapy. These include high dose prednisolone, cyclophosphamide, azathioprine, mycophenolate mofetil and cyclosporine; and recently the biologic rituximab therapy for refractory cases. This review focuses on the efficacy of tacrolimus, a potent

macrolide calneurin inhibitor with various cytokine modulating effects, and its role in lupus nephritis.
Material and methods: 2 experimental studies and 12 clinical publications on tacrolimus and lupus nephritis, including the author´s publications will be reviewed and presented. The author being the first to report the therapeutic success of tacrolimus in 6 adults SLE patients with relapsed lupus nephritis, will summarise data on the effectiveness of tacrolimus in class IV, class V lupus nephritis, and in class V+IV lupus nephritis (as part of multitarget therapy). Role of tacrolimus in induction therapy, maintenance therpay and in relapsed cases as a disease remitting agent will be discussed. Case illustrations will be presented and the cytokine modulating effects of tacrolimus will be summarised also.
Conclusion: Tacrolimus is an efficacious addition to the armamentarium of immunotherapy for lupus nephritis, and have a definite role as a first or second line immunoinductive therapy, and can used as part of a combination mutitarget immunosuppressive therapy in severe lupus nephritis.

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SERUM INFLIXIMAB LEVELS, ANTIBODIES TO INFLIXIMAB AND ALBUMIN CONCENTRATIONS DURING INFLIXIMAB TREATMENT IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES

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Aim: To determine the association of serum infliximab (S-IFX) disposition with the formation of serum antibodies to infliximab (S-ATI) and serum albumin levels (S-ALB).
Patients and methods: 85 patients who had inflammatory bowel disease (IBD) and were receiving infliximab treatment were included: 31 with ulcerative colitis (UC) and 54 with Crohn's disease (CD), age 36±12 years. Serum samples from the second (W2) and fourteenth (W14) weeks of treatment were assessed for S-IFX, S-ATI and S-ALB.
Results: S-IFX levels in W2 were significantly lower than in W14 (p=0.016). S-IFX levels were significantly higher in responders than in non-responders at W2 and W14 (p=0.011 and p=0.0006, respectively).
S-ATI were positive in 8/85 patients (9%) in W2 and 14/85 patients (17%) in W14. Absolute values of ATI concentrations were higher in W14 (p=0.018). S-ATI were significantly more common in samples with non-detectable S-IFX (p<0.0001). The highest values of S-ATI were found in patients who experienced the adverse effects of treatment (p=0.01). S-ALB levels were significantly lower in W2 than in W14 (p=0.0008). A strong positive correlation between S-ALB and S-IFX was found (r=0.39, p<0.0001). Albuminaemia in patients with detectable S-IFX was higher than in sera without detectable S-IFX (p<0.0001).
Conclusions: S-IFX correlate with clinical response to treatment with infliximab and S-ALB levels, whereas positive S-ATI are connected with the adverse effects of treatment and occur in sera without detectable S-IFX.
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IMPACT OF ACUPUNCTURE BY USING LIFE-ENERGY (QI, 氣) ORIENTAL NEEDLE ON THE PARALYSIS OF RATS WITH EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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In acupuncture, adaptation to energy flows in body cycles is the key to health and therapy. From the evolution of our thinking about acupuncture, we developed the Life-Energy (Qi) oriental needle (Qi needle). It contains a rotating electromagnetic wave. It has a strong affinity for the meridians. We report for the first time the activity of acupuncture by using Qi needle on rat experimental autoimmune encephalomyelitis (EAE), a model of human demyelinating multiple sclerosis, was tested. Both Qi acupuncture (QA) and general acupuncture (GA) and was stimulated on the limbs, shaoshang (LU11) and zhongchong (PC9) acupoints, on rats from 1 day post-immunization (dpi) to 14 dpi. QA groups significantly blocked the onset of EAE paralysis (2/5, 60%, p<0.05) while all rats in control EAE groups (6/6) and GA groups (5/5) showed EAE paralysis. The duration of paralysis was also shorten in QA groups (0.4±0.4 days) compared with those of vehicle (5.5±0.2 days) and GA groups (3.6±1.1 days). The number of inflammatory perivascular cuffing foci in QA treated EAE was significantly reduced compared with those of EAE control and EAE with GA (p<0.05). Collectively, the present finding suggests that QA ameliorate the paralysis in a rat EAE model. The precise mechanism on the amelioration needs further study.

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PEGYLATED INTERFERON-A, RIBAVIRIN AND RITUXIMAB COMBINED THERAPY OF HEPATITIS C VIRUS-RELATED MIXED CRYOGLOBULINEMIA: A LONG-TERM STUDY

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This study illustrates the use and efficacy of a combination of pegylated interferon-α (Peg-IFN-α) and ribavirin (RBV), with or without rituximab (RTX), a chimeric monoclonal antibody directed to CD20 antigen in hepatitis C virus (HCV)-related mixed cryoglobulinemia (MC). Twenty-two patients with HCV-related MC received Peg-IFN-α (2a: 180 μg or 2b: 1.5 μg/kg) weekly plus RBV (1,000 or 1,200 mg) daily for 48 weeks, and RTX (375 mg/m^2) once a week for one month followed by two five-monthly infusions (PIRR for short). Fifteen additional patients received Peg-IFN-α/RBV with the same modalities as the PIRR schedule. Complete response was achieved in 54.5% (12/22) and in 33.3% (5/15) patients who received PIRR and Peg-IFN-α/RBV respectively (p<0.05). Clearance of HCV RNA and conversion of B cell populations from oligoclonal to polyclonal in the liver, bone marrow and peripheral blood was maintained for up to 3 years in 10/12 (83.3%) and in 2/5 (40%) patients receiving PIRR and Peg-IFN-α/RBV respectively (p<0.01). Cryoproteins in 22.7% (5/22) patients with PIRR and in 33.3% (5/15) with Peg-IFN-α/RBV persisted despite sustained HCV RNA clearance. No response occurred in the remaining 5 patients of both groups. It is concluded that PIRR therapy is well tolerated and more effective than Peg-IFN-α/RBV combination in HCV-related MC. Its effect may last for over 3 years.

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ANTIMALARIALS -INDUCED HAIR DEPIGMENTATION

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Antimalarials-induced hair hypopigmentation (namely by Chloroquine) was first observed bY Alving, *et al*. about 50 cases have been reported, but none within the past 10 years (except for 1 case reported on march 2009 in sao Paulo, Brazil by Di Giacomo *et al*.). We report herein a case of Hydroxychloroquine -induced diffuse hair hypopigmentation following a chronic use of Hydroxychloroquine in a 30-year-old patient with diagnosed as Systemic Lupus Erythematosus. The patient presented complete recovery of normal hair colour after dosage reduction. On January 2009, the patient noticed hair and eyelash discolouration which is not accompanied by any symptoms or any clinical signs. Physical examination showed a 1-cm band of white depigmentation in the proximal portion of most scalp hairs. Eyelashes, eyebrows and body hair were also affected. The HCQ dosage was then reduced to 200 mg/day without discontinuation. After 2 months,normal coloured light brown hair growth could be observed proximally to the hypopigmented bands and the patient presented no further complications during follow-up. After 4 months, the white band of hair was eliminated by a haircut.on. On the basis of these effects in the pigmentary system, chloroquine is now being studied as an agonist for alkylating benzamides in the treatment of malignant melanoma metastases, research field in therapeutics opening a new research field in therapeutics.

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PRELIMINARY REPORT ON THE EFFECTIVENESS OF TOCILIZUMAB IN STILL DISEASE

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Objective: To describe our experience in treating with Tocilizumab two patients with refractory adult-onset Still disease (AOSD) diagnosed according to Yamaguchi criteria.
Case report: We describe two cases of AOSD diagnosed in 2002 and 2004, respectively. At onset patients' clinical history were characterized by intermittent fever, arthralgias, myalgias and asthenia associated with leukocytosis, elevated erythrocytes sedimentation velocity (ERS) and protein C reactive (PCR) levels. Infective markers, antinuclear antibodies (ANA) and rheumatoid factors (RA) were negative in both cases. Splenomegaly associated with multiple intra-abdominal lymphoadenopathies was present in Case 2. The first patient was successfully treated with prednisone (PDN) and methotrexate (MTX). However, two years after, the disease relapsed. She was thus treated with Anakinra, with initial clinical response. The

other patient was initially treated with oral prednisone associated with monthly infusive cycles of intravenous immunoglobulin (IVIg) (2g/kg) for six months. After an initial response, even this patient experienced a new flare of the disease. They were given Tocilizumab (8 mg/kg e.v.) with oral prednisone. Response to the treatment was evident in few weeks with resolution of fever, improvement of arthralgias and normalisation of laboratory parameters. At last follow-up at six months, the disease was still in remission. No side effects were seen
Conclusions: Our two cases suggest the effectiveness of Tocilizumab as optional treatment in patients with AOSD refractory to conventional therapies.

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SUCCESSFUL APPLICATION OF SUBCUTANEOUS IMMUNOGLOBULIN IN SEVERE INFLAMMATORY MYOPATHIES

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Aim: We have previously described the efficacy of the subcutaneous Ig administration (SCIg) in two subjects with polymyositis and with difficult vein access. We here extend our study to eight patients with refractory polymyositis (PM) and dermatomyositis (DM).
Patients and methods: Eight patients (6F and 1M) with PM (3) and DM (5) with a mean age of 55 years and a mean disease duration of 78 months. All of the patients received a more than two immunosuppressants before the treatment protocol. Their disease was considered refractory due to the presence of refractoriness to steroid and/or immunosuppressants or steroid-dependency. Mean follow-up, after the treatment start, was 18±3 months.
Results: SCIg was administered by a programmable pump, following a standardized protocol of infusion and changing the sites of administration. After a training period of in-hospital therapy, patients were switched to home management. The weekly dose was 0.2g/kg/week. We documented improvement of serum CK levels, MRC score and Rankin modified score with a reduction in daily prednisone dose. No adverse events nor local reactions in the infusion sites were described.
Conclusion: Our preliminary documented the effectiveness and the good tolerance of SCIg in active and severe myopathies. A longer follow-up period is necessary to evaluate their efficacy in alternative to IVIg treatment in inflammatory myopathies.

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SERONEGATIVE AND SEROPOSITIVE RHEUMATOID ARTHRITIS (RA): SIMILAR RESPONSE TO TNF INHIBITOR (TNFI) (ADALIMUMAB)

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Background: Few prognostic markers of a poor outcome in rheumatoid arthritis (RA) patients have been identified. The erosive disease, a high HAQ score and rheumatoid factor (RF) are linked to a less favourable course. No data have been published on the value of autoantibodies status at baseline and response to treatment with TNFI.
Objective: To evaluate whether the autoantibody status at the beginning of the treatment would influence the response to Adalimumab (ADA) at 6 months follow-up.
Methods: 122 patients (101 F; 39 early-RA, 83 long standing-RA; age 53.1±12.6 years; 86 seropositive: 28% CCP +, 10.5% CCP and RFIgA +, 17.4% CCP and RFIgM +; 30.2% CCP, RFIgM and RFIgA +, 2.3% CCP-, RFIgM and RFIgA +) with RA, not responsive to DMARDs therapy, received ADA (40 mg every 2 week) and were followed for six months. The clinical, biochemical and autoantibodies (anti-CCP, RFIgA, RFIgM) variables were collected over time. For every patient DAS was calculated at 6 month FU (good response: DAS<2.4).
Results: The Good EULAR response was reached at 6 month in 49 (57%) seropositive and 15 (41.7%, p=0.13) seronegative RA patients. No difference was seem in autoantibodies level between good and poor responders at the beginning of therapy. The reduction in RFIgM titles at 6° month correlated inversely with DAS score at T6 (r=0.58; p=0.01) .
Conclusions: The autoantibody status does not influence the response to ADA treatment. The percentages of Good EULAR response are similar in the seropositive and seronegative RA patients.

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EVALUATION OF PERILLA FRUTESCENS VAR. ACUTA KUDO AND ROSMARINIC ACID ON ALLERGIC RHINITIS AND ALLERGIC RHINOCONJUNCTIVITIS

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Allergy is characterized by the overreaction of the immune system. *Perilla frutescens* leaf extract has been reported to exhibit anti-allergic inflammatory activity. To investigate precisely the effect and its mechanism of 30% ethanol extract powder of *Perilla frutescens* var. acuta Kudo (EPPF) and rosmarinic acid (RA), component of EPPF in allergic rhinitis and rhinoconjunctivitis. The number of nasal, ears, and eyes rubs after the ovalbumin (OVA) challenge in the OVA-sensitized mice was significantly higher than that in the OVA-unsensitized mice. Increased number of rubs was inhibited by administration of EPPF or RA. Increased levels of IgE in serum, spleen, and nasal mucosa of the OVA-sensitized mice were reduced by EPPF or RA administration. Histamine level was reduced by EPPF or RA administration in serum of the OVA-sensitized mice. Protein levels and mRNA expressions of IL-1β, IL-6, and TNF-α were inhibited by EPPF or RA administration in nasal mucosa tissue or spleen of the OVA-sensitized mice. In the EPPF or RA-administered mice, mast cells and eosinophils infiltration increased by OVA-sensitization was decreased. In addition, EPPF or RA inhibited the cyclooxygenase-2 protein expression and caspase-1 activity in same nasal mucosa tissue. In activated human mast cells, the NF-κB/*Rel A* and caspase-1 activation increased whereas NF-κB/*Rel A* and caspase-1 activation was inhibited by treatment of EPPF or RA. These results indicate that EPPF and RA ameliorate the allergic inflammatory reactions such as allergic rhinitis and allergic rhinoconjunctivitis.

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ALLEVIATION OF ALLERGIC RHINITIS SYMPTOMS WITH PYEONGWEE-SAN

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Allergy is characterized by the hyper-reaction of the immune system. Pyeongwee-San (KMP6) is traditional Korean medicine has been the treatment of the digestive system. However, KMP6 has been clinically used the regulation of allergic reaction. To investigate the new anti-allergic effect of KMP6, we compared with Hansin-Pyeongweesan (HS-PS), HES, dexamethasone (DEX), hesperidin (HES) the active component of HS-PS, KMP6, HES and DEX in allergic rhinitis model. The number of nasal, ears, and eyes rubs after the ovalbumin (OVA) challenge in the OVA-sensitized mice was significantly higher than that in the OVA-unsensitized mice. Increased number of rubs was inhibited by administration of KMP6, HS-PS, HES, and DEX. Increased levels of IgE and histamine level in serum of the OVA-sensitized mice were reduced by KMP6, HS-PS, HES, and DEX-administration. Protein levels of IL-1β, TNF-α, MIP-2, and ICAM-1 were inhibited by KMP6, HS-PS, HES, and DEX-administration in nasal mucosa tissue of the OVA-sensitized mice. In the KMP6, HS-PS, HES, and DEX-administered mice, eosinophil and mast cell infiltration increased by OVA-sensitization was decreased. In addition, KMP6, HS-PS, HES, and DEX inhibited the COX-2 protein expression in same nasal mucosa tissue. These results indicate that KMP6, HS-PS, HES, and DEX ameliorate the allergic inflammatory reactions such as allergic rhinitis and allergic rhinoconjunctivitis.

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SINGLE DOSAGE OF RITUXIMAB INDUCES REMISSION IN EARLY WEGENER GRANULOMATOSIS

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Wegener granulomatosis (WG) is a multisystem autoimmune disease characterized by small vessel inflammation and autoantibody /ANCA production.
A latest study has been shown that B-cell depletion with rituximab (375 mg per square meter of body-surface area per week for 4 weeks) is able to induce remission in relapsing WG.
We examined a retrospective collective of 11 patients from the last five years of our clinic with WG with ENT and pulmonal and/or renal affection. 7 patients (group A) had relapsing disease despite of prior treatment with cyclophosphamid or MMF (mean disease duration 72 months). 4 patients (group B) had new onset WG and

were therapy naive (mean disease duration 4 months). All patients received rituximab in the mentioned dosage. 8 patients had renal and 9 patients had pulmonary disease, 8 had affection of both organs. Maintenance consisted of glucocorticosteroids in both groups. Patients in group B additionally had MMF.
5 of 7 patients with relapsing disease had a new relapse after median of 12 months, whereas in new diagnosed patients 3 of 4 patients remained in remission up to now, defined as the absence of disease symptoms and reduction of steroid dosage under 7,5 mg prednisolone. Patients in remission received rituximab after another in median 6 months, irrespective of B-cell counts.
To conclude, a single dose of rituximab, repeated after 6 months in combination with MMF seems to be an option for patients with early WG with renal and/or pulmonary involvement and is able to sustain remission.

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BELIMUMAB, A BLYS-SPECIFIC INHIBITOR, REDUCES DISEASE ACTIVITY AND SEVERE FLARES IN SEROPOSITIVE SLE PATIENTS: BLISS-76 STUDY

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Objective: To assess the efficacy and safety of belimumab in seropositive SLE patients (pts).
Methods: In BLISS-76, a 76-wk double-blind, international, phase 3 study, 819 seropositive SLE pts (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) with SELENA-SLEDAI (SS) score ≥6 on stable therapy (≥30d) were randomized to belimumab (1 or 10mg/kg iv) + standard of care (SOC) vs placebo plus SOC on d 0, 14, 28, then q28d for 72 wks. Efficacy analyses included SS, BILAG, and SS Flare Index (SFI). Primary endpoint was % SLE Responder Index (SRI) response at 52 wks: SS improvement (≥4-point decrease), no new BILAG 1A/2B flares, and no >0.3-point Physician's Global Assessment (PGA) worsening vs baseline.
Results: Mean values for baseline disease characteristics across treatment groups were similar: disease duration 7.5 yrs; antimalarial use 63%; steroid use 76% with prednisone-equivalent dose of steroid ≥7.5mg/d in 46%; immunosuppressant use 56%; proteinuria (>0.5g/24hr) 16%; low C4 53%; SS 9.7; BILAG 1A/2B 64%; ANA+ 92%; anti-dsDNA+ 64%. SRI response rates were 34% on placebo, 41% on 1mg/kg (p=0.104 vs placebo) and 43% on 10mg/kg belimumab (p=0.021 vs placebo). Significant improvements were also seen in at least 1 of the belimumab groups for: SS ≥4-point reduction; no >0.3-point worsening in PGA; reduction in severe flares; improvement in SF-36 Physical Component Summary, and FACIT-Fatigue.
Conclusion: In BLISS76, belimumab significantly improved the SRI response rate and reduced SLE disease activity and severe SLE flare rates in seropositive SLE pts. AEs were comparable in the belimumab and placebo groups.

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RITUXIMAB IN SYSTEMIC LUPUS ERYTHEMATOSOUS: THE ITALIAN MULTICENTER REGISTRY

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We evaluated safety and efficacy of Rituximab (RTX) in refractory systemic lupus erythematosous (SLE).
Eighty-one SLE patients, 67 women, mean (±SD) age 40.4 (±11.97) years, mean disease duration 12.1 (±7.42), were treated with RTX (Rheumatoid schedule in 63 cases, haematological schedule in 18 cases) plus corticosteroids and immunosoppressants. Refractory manifestations were articular 53 cases (65.4%), haematological 48 (59.3%), renal 44 (54.3%), cutaneous 39 (48.1%), neuropsychiatric 9 (11.1%) and serosal 18 (22.2%).
Median follow-up after treatment was 13.3 months (range 4-60). Mean ECLAM score was 3.84 at baseline vs 1.98 at 3 months (p<0.01), 1.61 at six months (p<0.01), and 2.02 (p<0.01) at 12 months. In patients with glomerulonephritis, mean (±SD) 24-hour proteinuria was 3.2(±2.6) g at baseline vs 1.64(±1.96) g at 3 months, 0.98(±1.1) g at 6 months, and 0.50(±0.49) g at 12 months.
Thirty-four patients were retreated after a median period of 13.7 months (range 3-34). Mean ECLAM score was 3.17 at the re-cycle baseline vs 1.50 at 3 months (p<0.01), 1.81 at six months (p<0.05). In patients with glomerulonephritis, mean (±SD) 24-hour proteinuria was 1.57(±1.45) g at re-cycle baseline vs 0.47(±0.58) g at 3 months, 0.70(±0.59) g at 6 months, and 1.04(±1.19) g at 12 months.
Adverse events were observed in 10/81 cases: 1 infusion reaction, 7 infections, 2 hypogammaglobulinemia. At re-cycle adverse events were 8/34 cases: 2 infusion reactions, 2 skin rash, 2 infections, 1 serum sickness, 1 hypogammaglobulinemia.
In conclusion, RTX seems to be safe and effective in refractory SLE patients.

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OVERACTIVE LIFESTYLE IN FIBROMYALGIA AS A CORE FEATURE OF BIPOLAR SPECTRUM DISORDERS

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Background: We hypothesized that the overactivity described in patients with fatigue and pain represents the core feature of manic/hypomanic symptoms characterizing the bipolar spectrum disorders. To evaluate this hypothesis we used an emerging innovative framework for bipolar spectrum disorders.
Method: 100 outside patients with fibromyalgia (FM) were assessed for bipolar spectrum disorders utilizing two different approaches: the first based on a version of DSM-IV SCID- CV interview modified to improve the detection of bipolar spectrum disorders and the second based on the hypomania symptoms checklist HCL-32.
Results: High rates of bipolar spectrum disorder were identified according to the SCID-CV modified version in 91 (91%) patients with FM. 60/100 patients (60%) had a major bipolar spectrum disorder, mainly a bipolar II disorder, and 31 patients (31%) had a minor bipolar spectrum disorder represented by the minor bipolar disorder and the pure hypomania (according to Angst definition). No difference in demographic and clinical aspects between FM patients with a major depressive episode (the major bipolar spectrum) and those with minor bipolar spectrum disorders was observed.
Hypomanic symptoms evaluated by HCL32 confirmed a high estimates of bipolar spectrum, with a 85% of subjects scoring a 14-or-more-items threshold for hypomania.
Conclusions: Overactivity considered as core feature of hypomanic symptoms associated to bipolar spectrum disorders, seems to be common in FM patients. Different degrees of severity of mood disorders are not related to demographic and clinical characteristics of FM patients, suggesting that the psychiatric disorders may have a role per se.

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FINANCIAL COMPENSATION, RECOVERY AND RETURN-TO-WORK FOR LOW BACK PAIN PATIENTS TREATED IN SPINE CLINICS

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Objective: To investigate clinical and vocational outcome years after low back pain episodes in relation to financial claims and other potential risk factors of chronic pain and disability in patients with low back pain.
Methods: A prospective outcome in two Danish, non-surgical spine clinics. Patients with low back pain (n=1243) were referred to the clinics by their general practitioners. Rheumatologists, physiotherapists, and nurses examined, treated, and informed the patients based on cognitive principles. Follow-up data were collected with a postal questionnaire after 1 year and by registries after 5 years. Claim, defined as seeking some sort of financial compensation such as workers' compensa-

tion, was the main independent variable. Potential confounders examined were: age, sex, social class, smoking, duration and severity of pain and disability. The main outcome measures were: global assessment after 1 year and not returning to work after 5 years.
Results: Financial claims were registered for 31% of patients. After adjustment for confounders, the odds ratios for claim at baseline and no clinical improvement after 1 year, were calculated to be 4.2 (95% CI 2.8-6.2) and 2.1 (1.5-3.0) of not returning to work at 5 years.
Conclusion: A claim for financial compensation is strongly and independently linked with a poor clinical prognosis after 1 year and poor vocational recovery after 5 years.

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THE ASSOCIATION OF FINANCIAL COMPENSATION WITH PAIN AND VOCATIONAL RECOVERY FOR NECK PAIN PATIENTS TREATED IN SPINE CLINICS

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Objective: To investigate clinical and vocational outcome years after neck pain episodes in relation to financial claims and other potential risk factors of chronic pain and disability in patients with neck pain.
Methods: A prospective outcome study with internal control groups in two Danish, non-surgical spine clinics. Patients with neck pain (n=202) were referred to the clinics by their general practitioners. Rheumatologists, physiotherapists, and nurses examined, treated, and informed the patients based on cognitive principles. Follow-up data were collected with a postal questionnaire after 1 year and by registries after 5 years. Claim, defined as seeking some sort of financial compensation or filing any sort of financial claim, such as workers' compensation, was the main independent variable. Potential confounders examined were: age, sex, social class, smoking, duration and severity of pain and disability.
The main outcome measures were: Global assessment (main outcome variable), pain, disability, and intake of analgesics after 1 year and not returning to work after 5 years.
Results: Financial claims were registered by 25% of patients. After adjustment for confounders, the odds ratio for claim at baseline and no clinical improvement after 1 year, was calculated to be 17.4 (95% CI 5.1-60.1) and 4.4 (1.7-11.5) of not returning to work at 5 years.
Conclusion: A claim for financial compensation is strongly and independently linked with a poor clinical prognosis after 1 year and poor vocational recovery after 5 years.

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TUMORAL CALCINOSIS IN CHRONIC RENAL FAILURE: CLINICAL AND THERAPEUTICAL APPROACH

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Introduction and aims: Tumoral calcinosis is a rarely observed form of extraskeletal calcification which is often invalidating in patients with chronic renal failure. Their pathogenesis remains poorly understood and their management is badly codified. We propose a clinical and therapeutic approach of a new case of several juxta-articular tumoral calcinosis in extra-skeletal tissue.
Methods: A 26-year-old patient with an end stage kidney failure secondary to IgA nephropathy on maintenance haemodialysis for 3 years, who presents since 6 months a polyarthralgia interesting large and small joints which progressing to the appearance of juxta-articular soft masses which become so large with skin ulceration and sinus tracts draining chalky milk material. Clinical examination and morphological assessment had revealed calcified masses, which contour were lobuled, with an infiltration of periarticular hypodermis and muscles of the shoulders, elbows, knees, metacarpals, metatarsals and coxo-femoral and inter-phalange joints.The patient had a tertiary hyper-parathyroidism: with parathyroid hormon (PTH) 898pg/ml, serum calcium 109mg/l, serum phosphate 82mg/l, high calcium-phosphorus product (CaPh) 8938mg/l, normal total phosphatase alkalin 110 UI/l, and normal 25 hydroxyvitamin D3 24 IU/ml.The serum protein electrophoresis, bacteriological and immunological investigations were negatives and skin biopsy objectived cutaneous and muscular calcium deposits.
Results: The patient received daily sessions of dialysis (6 times/week of 4 hours) by low-calcium bath (1.37 mmol/l) followed by 7/8 th parathyroidectomy (PTX) allowing a correction of phospho-calcium balance with a postoperative control PTH at 31pg/ml and spectacular decline of the size of calcinosis on the fifteenth day.

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DETECTION AND IDENTIFICATION OF MYCOBACTERIA AND GENES ASSOCIATED TO MYCOBACTERIUM *TUBERCULOSIS* AND *BOVIS* IN AORTAS OF PATIENTS WITH TAKAYASU'S ARTERITIS

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Objectives: Takayasu's arteritis (TA) is a chronic inflammatory disease affecting the large arteries and their branches; its etiology is still unknown. Arterial inflammation is subclinical, progresses to stenosis and/or occlusion, leading to organ damage and affecting prognosis and survival. A relation of TA with *Mycobacterium tuberculosis* has been informed. Our objective was to search for sequences of genes associated to mycobacteria in aorta tissues from autopsies of TA cases.
Material and Methods: We chose aorta tissues embedded in paraffin from autopsies of patients with TA according to the American College of Rheumatology (ACR) criteria. We formed two control groups one with tuberculosis and other with atherosclerosis, blinded to the deparaffinizing procedures. DNA was extracted and amplified and we analyzed the IS6110 and HupB gene sequences.
Results: Of 181 selected, 119 fulfilled the criteria, 33 corresponded to TA, 33 to tuberculosis (TB), and 59 to atherosclerosis. Average age for each group was 22±13, 41±19, and 57±10, respectively Tandem repeats of gene *IS6110* and sequences of gene *HupB* through nested PCR were 23 (70%) for *M. tuberculosis* in TA, and 27 (82%) in TB vs. controls with atherosclerosis 19 (36%); p=0.004 and 0.0000, respectively. Nested PCR for *M bovis* did not reveal any differences among groups.
Conclusion: We identified genes associated to *Mycobacterium tuberculosis* in aorta tissues from patients with TA. The arterial damage could be an extra pulmonary tuberculosis. Our findings allow us to propose new study hypotheses and therapeutic management strategies.

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VARIATIONS IN ATHEROSCLEROSIS MARKERS DURING TOCILIZUMAB TREATMENT IN RHEUMATOID ARTHRITIS: PRELIMINARY RESULTS

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Background: Rheumatoid arthritis (RA) is characterized by an increase in cardiovascular (CV) mortality.
We compared different markers of accelerated atherosclerosis in patients with RA at baseline and after 3 months of treatment with TCZ (dose 8 mg/kg every 4 weeks).
Methods: 16 RA outpatients (all females; mean age 56±9.3 yrs) with active disease who started treatment with TCZ were included in this prospective study.We detected cytokines (TNF-α, IL-6, IL-10, IL-8), acute phase proteins (ESR , CRP, Serum Amyloid A), lipid profile (total cholesterol (TC), Triglycerides (TG), HDL, LDL, LPa), endothelial and coagulation markers (PAI-1, von-Willenbrand, β2GPI, F1+F2) and CD4+/CD28-T cells at baseline and after 3 months.According to DAS28 values the patients were classified in remission for DAS28 < 2.6 and having low disease activity for DAS28 range between 2.6-3.2.
Results: After 3 months 10 patients were considered to be in remission (group A) and 6 patients as having low disease activity (group B). Between these two groups a significant difference was found in the following parameters: ESR (12,6±3.2 vs 28,5±4,8 mm/h, p<0.05); CRP (0,8±0,4 vs 1,8±0,4 mg/dl, p<0.05); SAA (6,2±2,4 vs 13,3±3,4 mg/dl, p<0.05); CD4+/CD28- cells (0,4±0,2 vs 1,3±0,4 cells/mL, p<0.01); IL-6 (26,3±11,4 vs 9,6±3,5 pg/ml, p<0.05); TNF-α (13,1±2,4 vs 26,2±3,5 pg/ml, p<0.01). No differences on lipid profile and coagulation markers were observed.
Conclusion: This study shows that a 3-month treatment with TCZ not only decreases inflammation, but also reduces circulating CD4+/CD28- cells, which are known to play an important role in accelerated atherosclerosis.