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Challenges in the treatment of Rheumatoid Arthritis

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ABSTRACT

Rheumatoid Arthritis (RA) is a chronic inflammatory disease characterized by a heterogeneous clinical response to the different treatments. Some patients are difficult to treat and do not reach the treatment targets as clinical remission or low disease activity. Known negative prognostic factors, such as the presence of auto-antiantibodies and joint erosion, the presence of a genetic profile, comorbidities and extra-articular manifestations, pregnancy or a pregnancy wish may concur to the treatment failure. In this review we aimed at identify difficult to treat RA patients and define the optimal therapeutic and environmental targets. Genetic markers of severity such as HLA-DRB1, TRAF1, PSORS1C1 and microRNA 146a are differently associated with joint damage; other gene polymorphisms seem to be associated with response to biologic disease modifying anti-rheumatic drugs (bDMARDs). The presence of comorbidities and/or extra-articular manifestations may influence the therapeutic choice; overweight and obese patients are less responsive to TNF inhibitors. In this context the patient profiling can improve the clinical outcome. Targeting different pathways, molecules, and cells involved in the pathogenesis of RA may in part justify the lack response of some patients. An overview of the future therapeutic targets, including bDMARDs (inhibitors of IL-6, GM-CSF, matrix metalloproteinases, chemokines) and targeted synthetic DMARDs (filgotinib, ABT-494, pefacitinib, decernotinib), and environmental targets is addressed. Environmental factors, such as diet and cigarette smoke, may influence susceptibility to autoimmune diseases and interfere with inflammatory pathways. Mediterranean diet, low salt intake, cocoa, curcumin, and physical activity seem to show beneficial effects, however studies of dose finding, safety and efficacy in RA need to be performed.

1. Identify difficult to treat RA

Heterogeneous clinical phenotypes, different patterns of response to therapy and mosaic severity disease among RA patients had raised the need among clinicians to identify possible response predicting factors and profile single RA patient conditions.

1.1. Genetic risk factors

Genetic biomarkers have been investigated in several studies to determine whether a personalized approach, based on individual characteristics, might be possible. > 100 genes variants are known to promote the risk of developing RA and, among these, the main influence is linked to HLA-DR (HLA DR1 and HLA DR4) [1]. The molecules encoded by the risk allele HLA-DRB1 share a conserved 5-aminoacid sequence that is associated with the development of anti-citrullinated protein antibodies (ACPA), leading to the genesis of the "shared epitope" hypothesis [2]. The identification of genetic markers of severity is debated since the definition of severity is not standardized and the disease outcome changes over time being influenced by several confounding factors. The presence of HLA-DRB1 alleles seems to predict radiographic damage, which may be partially mediated by ACPA development, and also elevated sera inflammatory levels and high swollen joint count [3–5]. Genetic markers of severity may be different between ACPA-positive and ACPA-negative RA. Apart from HLA loci, SNPs located near TNF receptor-associated factor 1 (TRAF1) have been associated with radiographic damage in several independent cohorts [6]. Ciccacci et al. investigated a total of 12 SNPs and related them to presence of Rheumatoid Factor (RF), ACPA and clinical phenotype in a cohort of 192 biologic drugs naïve Italian RA patients. SNPs in the gene psoriasis susceptibility 1 candidate 1 (PSORS1C1) and microRNA 146a (MIR146A) were protective regarding the presence of bone erosions and RF respectively; meanwhile SNPs in the gene protein tyrosine phosphatase non-receptor type 2 (PTPN2) were associated with a severe disease phenotype in terms of radiographic damage [7]. Another SNP located in the Forkhead Box O3A (FOXO3A) gene region has been

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described as associated with worst disease course in several TNF-mediated conditions, including RA. The minor allele at FOXO3A induces a differential response of monocytes in RA patients with a consequent increase in the production of pro-inflammatory cytokines, including TNFα [8]. Moreover, epigenetic changes had recently been identified as a crucial link between genetic and disease risk [9]. Epigenetic is defined as heritable changes in the genome that are independent from the DNA sequence and can control genes expressions influencing disease risk, prognosis and drug response [10]. DNA methylation studies suggest that differentially methylated genes could alter fibroblast-like synoviocytes (FLS) gene expression and contribute to the pathogenesis and severity of RA. In RA synovium, FLS assume an aggressive phenotype that contributes to joint damage and can evolve throughout the timing of the disease, as late RA cells are related to a more aggressive pattern of synoviocites than early RA ones. Evidence suggests that several SNPs are involved not only in the subset of RA, but might also be adopted as predictive factors of response to therapy [7]. The interest in building a personalized medicine has led many studies investigating possible gene polymorphisms associated with response to TNF inhibitors (TNFi): the presence of specific SNPs in STAT4, PTPN2, PSORS1C1 and TRAF3IP2 genes seemed to correlate with a better response to TNFi treatment in a group of Italian RA patients [11]. However, despite recent discoveries, several meta-analysis demonstrated that SNPs failed to improve prediction of response to TNFi when added to standard markers as sex, age and methotrexate use [12]. MicroRNAs generally act as negative regulators of the expression of their target proteins, and their increase after biologic disease modifying anti-rheumatic drugs (bDMARDs) combination has been associated to a reduction in the inflammatory serum markers and to improvement of the overall disease status of patients [13]. Overall no genetic variants have yet been robustly and consistently associated with response to therapies used in RA. Identification of targeted bDMARDs therapies still remains unsatisfied as disease outcome derives from the combination of both genetic and environmental factors.

1.2. Multifailure

In clinical practice not all the patients gain low disease activity (LDA) and clinical remission, therefore discovering reasons behind therapy failure has become one of the most important issues for rheumatologists [14,15]. As recently evidenced by an international survey conducted among rheumatologists a 5–20% of patients are difficult-to-treat despite treatment according to European League Against Rheumatism (EULAR) management recommendations. The presence of some characteristics in these patients were identified such as moderate disease activity, comorbidities, extra-articular manifestations, inability to taper corticosteroids, fatigue and failure of 2 or more conventional synthetic (cs)DMARDs and/or bDMARDs [16]. TNFi failure is one of the most studied in RA patients. In a retrospective Italian cohort of 308 RA patients treated with TNFi, 60% of study population did not reach clinical remission. The main positive predictors for failing to reach LDA or clinical remission were: male gender, age at the time of TNF-i treatment ≤ 54 years, negative baseline C-reactive protein (CRP) and concomitant csDMARDs, while the presence of any comorbidity resulted to be a negative predictor of remission/LDA [17,18]. Mathematical models to estimate patient's clinical response during therapy and profile changes in gene expression of peripheral blood mononuclear cells in responders to bDMARDs could predict the efficacy of specific treatment [19,20]. The presence of comorbidities remains a major issue in many patients and a limitation in the choice of pharmacological therapy; comorbidity becomes not only a limitation but also a risk factor for a worst prognosis [21].

1.3. Comorbidities and extra-articular manifestations

RA should not be considered merely a “joint disease” because of comorbidities and extra-articular manifestations, the last occurring in about 40% of patients at any time during the course of the disease [22]. High body mass index (BMI) in RA can have a significant negative impact on clinical outcomes, such as a high prevalence of chronic pain and depressive symptoms [23]. Moreover, a correct assessment of disease activity may be difficult in overweight and obese RA patients. Goossens J et al. showed that both swollen joint count and disease activity score (DAS) might be underestimated by clinical assessment in RA patients with high BMI when compared to ultrasound [24]. The response to treatment seems to be influenced by BMI and varies among bDMARDs. Overweight and obese patients are usually less responsive to TNFi and have worse clinical course [25,26]. Recently, abatacept and tocilizumab demonstrated clinical efficacy independently of BMI. Despite IL-6 is known to have paradoxical role in metabolic processes, serum IL-6 is elevated in obese patients resulting in hepatic insulin resistance. The use of tocilizumab in RA patients has been associated with the reduction of the HbA1c level [27,28,29]. RA has long been associated with accelerated atherosclerosis and increased cardiovascular diseases (CVD). Atherosclerosis is a recognized chronic inflammatory condition sharing cellular processes and cytokines with RA. Increased swollen joint count, CRP levels and disease duration seems to be associated with cardiovascular mortality in RA [30]. The presence of comorbidities may influence the treatment strategy and clinical outcomes [31]. Therefore, RA patients are closely monitored for pre-existing comorbidities and for the possible risk of developing new ones [32]. Treatment with bDMARDs has been associated with an increased risk of serious infections in data from randomized controlled trials and registries [33]. In this context an integrated approach may have a positive effect in the management of joint disease [34,35].

Extra-articular RA manifestations are severe conditions that should be aggressively treated and monitored when present [36]. Recognized risk factors for the presence of extra-articular manifestations are high titers of RF, ACPA and the presence of HLA DRB1*04 subtype [37–40]. Systemic manifestations seem to be linked to vasculitis that is associated with young age and smoking status at RA diagnosis, peripheral vascular disease, cerebrovascular disease, presence of bone erosions and rheumatoid nodules [41]. The management of extra-articular manifestations includes the use of glucocorticosteroids, cytotoxic agents, such as cyclophosphamide, and bDMARDs such as TNFi, and B-cell and T-cell-targeted therapies [42,43]. Rituximab seems to offer promising effect on interstitial lung disease [44,45]. However, the incidence of extra-articular manifestations is decreased, mostly due to more effective management of the underlying disease in the modern treatment era.

1.4. Pregnancy and lactation

Pregnancy in patients with rheumatic conditions can be a challenge for rheumatologist [46–48]. Highlights in the management of RA pregnant patients are: pre-conceptional counseling, assessment and control of disease activity before and throughout pregnancy, treatment and pregnancy outcome [49]. Historically, effects of pregnancy on inflammatory arthritis seemed to indicate a beneficial response, particularly for RA, while recent systematic analysis showed that about 60% of patients with RA improve during pregnancy [50,51]. Multiple studies report an increase risk of small-for-gestational-age (SGA) infants in RA women [52,53], as well as lower birth weight [54,55]. De Man et al. showed that seronegative RA patients are more likely to improve disease activity during pregnancy than patients positive to those [56]. According to the suppression of the maternal immune system, which occurs to induce tolerance against the fetus, it has been hypothesized that a higher genetic difference between maternal and fetal HLA class II in the DRB1, DQA and DQB alleles could induce a stronger suppression of maternal immune system improving RA disease activity, but these data have not been reconfirmed in following studies [57–59].

The reduced level of estrogens, which takes place during pregnancy,

seems to play a role in the improvement of the disease. Several studies supports the evidence of an altered mechanism of peripheral sex hormones synthesis in synovial tissue of RA patients: intracrine synthesis of active estrogen metabolites at the level of macrophages and fibroblasts results in increase of inflammatory cytokines production and consequent synovial inflammation and hyperplasia [60,61]. Determination of disease activity during pregnancy can be insidious as variants of the DAS including erythrocyte sedimentation rate (ESR) is influenced by pregnancy due to increased circulating fibrinogen, plasma expansion and decreased hemoglobin concentration. Pregnancy might also influence the visual analogue of global health, which is incorporated in the DAS [62,63]. Pre-conceptional counseling and risk assessment before attempting pregnancy should be performed in every woman with systemic autoimmune disease to increase the probability of success. Treatment of RA patients during pregnancy can be possible with reasonable safety for the child. Available data from literature and registries show that a large number of conventional medications can be taken by pregnant and lactating women: glucocorticoids, hydroxychloroquine, azathioprine and cyclosporine are universally considered safe and compatible with breastfeeding [64]. Non-fluorinated glucocorticoids, such as prednisone, are metabolized by the placenta and do not reach fetus, while fluorinated ones should be restricted to fetal indications, as, for example, the induction of fetal lung maturation [65]. Sulfasalazine is recommended with folate supplementation throughout the entire pregnancy, and can be used during breastfeeding but should be avoided in lactation of premature or ill infants [64]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are not teratogenic in first and second trimester, but after week 20 can impair renal function and cause constriction of the ductus arteriosus [66]. Their concentration in breast milk is very low and they are considered compatible with lactation [67]. Leflunomide is teratogenic in animal studies [68], but up to now there is no evidence of congenital malformations after first trimester exposure when followed by cholestyramine washout [68], but data are limited and its use is not recommended during pregnancy and breastfeeding. Methotrexate (MTX) is known to be teratogenic and to induce miscarriages; it should be stopped 3 months before a planned pregnancy [64,69] and should be avoided in lactating women as small amount in breast milk has been detected. TNF inhibitors may be continued at least in the first half of pregnancy as their use has not been associated with congenital abnormalities or adverse pregnancy outcome [70,71]. Infliximab, Adalimumab and Etanercept demonstrated binding to the fetal Fc receptor (FcRn) and were actively transported across the placenta, while Certolizumab Pegol showed no measurable transfer from the maternal to the fetal circulation because of its different molecular structure that does not contain any Fc region [71]. Evidence for fetal/child safety is still lacking for golimumab, abatacept and rituximab, but registry data do not suggest any evidence of harm when used before conception or in the first trimester [70]. TNFi are compatible with breastfeeding, as minimal transfer to breast milk has been shown for infliximab, adalimumab, etanercept and certolizumab [70]. Hoeltzenbein et al. analyzed clinical trials and post-marketing data on the safety of tocilizumab (TCZ) and concluded that there is no a substantial risk for malformations after exposure shortly before conception or early in the first trimester, but data are unclear about the increased rate of preterm birth and low birth weight children associated with TCZ exposure [72]. Emerging new molecules as tofacitinib and baricitinib are gaining attention on their use during pregnancy: a large population study showed that unintentional exposure to tofacitinib during conception/pregnancy does not appear to be associated with an increased risk to the fetus compared with general population. No information is available to support the use of baricitinib in pregnancy or lactation, as experience with small molecules is too small to draw any recommendation [73,74]. In conclusion, many treatment options are available for pregnant RA patients to assure optimal pregnancy outcome. The management of pregnancies in women with autoimmune conditions still represents a challenge and must be approached with a multidisciplinary point of view.

2. Optimal targets in RA

Despite the constant improvement in target strategies and the new drugs employed for the treatment of RA, some patients may still fail to respond. This can happen for different reasons as previously discussed. The choose of targeting different pathways, molecules, and cells involved in the pathogenesis of RA may in part justify the lack response of some patients. Hence, different are the compartments involved and to the same extent are the possible targets for treating RA. Therefore, it is definitely important to identify the optimal target for each patient, exploring the growing and interesting spectrum of precision medicine. In the last years, the treatments available grew in an impressive way. The treatments with a specific target currently available can be included in the bDMARDs, i.e. TNFi, costimulation modulators, IL-6-inhibitors, IL-1 inhibitors, and anti-B cell drugs, or targeted synthetic DMARDs (tsDMARDs), such as JAK-inhibitors. This research field is growing and new experimental target are under investigation, looking at both innate and adaptive immunity. In more detail, when the clinical remission or LDA are not achieved with csDMARDs, and poor prognostic factors are present a bDMARDs or tsDMARDs should be used [75]. Recently, the transcriptional targets have been developed. A novel and promising treatment for RA patients consists on the inhibition of different cytokines simultaneously by using the inhibitors of the Janus Kinase family (JAK) [76] such as tofacitinib, the first JAK-inhibitor approved for RA treatment that preferentially inhibits JAK-3 and -1 over JAK-2, and baricitinib that is selective for JAK-1 and -2 [77–80].

3. Beyond current and new treatments

3.1. Future therapeutic targets

The interest towards the role of the innate immunity in the pathogenesis of RA is growing. FLS, residential macrophages and dendritic cells are directly involved in the pathogenesis of RA. Accordingly, new drugs targeting these mediators are in phase of developing. GM-CSF is a cytokine stimulating the maturation of myeloid cells from the bone marrow, and it is fundamental for the function and maturation of several cells of the innate immunity, i.e. monocytes, macrophages, neutrophils, and dendritic cells [81,82]. Some GM-CSF inhibitors have reached the phase II-III in clinical trials for the treatment of RA which include MOR103, namilumab, lenzilumab, gimsilumab, and mavrilimumab [83–87]. The effectiveness of anti-GM-CSF in the treatment of RA confirm that the innate immune play an important role in the disease pathogenesis and targeting it may fill the gap we a facing in the treatment of non-responder patients. Recently also sarilumab, the second IL-6 inhibitor approved for the treatment of RA, demonstrated its superiority versus adalimumab in monotherapy [88] and it can bind IL-6 with higher affinity than tocilizumab. Further inhibitors of IL-6 are currently under investigations, such as sirukumab [89]. Other drugs are under development, such the inhibitors of matrix metalloproteinases that can be a promising new strategy in preventing joint destruction; a phase II clinical trial demonstrated that andecaliximab is safe and well tolerated in patients with RA [90]. Moreover, targeting the chemokines can prevent the migration of different immune cells both of innate and adaptive immunity. Thus, some chemokines inhibitors have been investigated with good preliminary results [91,92]. Furthermore, new JAK-inhibitors are under investigation. Filgotinib and ABT-494, two selective JAK-1 inhibitors, showed to be effective in patients with RA in association with a good safety profile and tolerability [93–95]. Also the JAK-inhibitor pefacitinib resulted effective and well tolerated in patients with moderate-to-severe RA in combination with csDMARDs [96]. Lastly, the selective JAK-3 inhibitor decernotinib demonstrated it efficacy in treating active RA both in association with csDMARDs and in monotherapy [97,98]. The potential drugs that can be used for the

treatment of RA are clearly growing with the hope of reducing the number of non-responder patients, in the meantime the attention of clinician dealing with should be focused on stratifying the risk and predict the response to these treatments, as well to treat the environmental and life style risk factors with the goal of reaching the remission in the highest number of patients.

3.2. Environmental targets

Environmental factors, particularly diet, may influence susceptibility to autoimmune diseases by epigenetic mechanisms such as DNA methylation and histone modification processes [99]. The diet can be a potential aggravating or protective factor for RA in symptomatic relief [100]. Evidence suggests that various foods may help in reducing levels of inflammatory cytokines in RA patients [101]. The Mediterranean diet, rich in plant-based foods such as wholegrains, legumes, fruit, vegetables, extra-virgin olive oil and low in red meat consumption, might have the potential to reduce the risk of RA [102,103]. An important component of mediterranean diet is olive oil that has antioxidant properties and anti-inflammatory effects similar to those of n-3 polyunsaturated fatty acids (PUFA) from fish oils [104]. There is evidence that PUFA supplementation has the potential to reduce inflammation and provides clinical benefit [103]. In the murine model of collagen-induced arthritis, the diet based on extra virgin olive oil has significantly reduced joint oedema and cartilage destruction, preventing the development of arthritis, compared to the use of other oils. Significant reduction in serum cartilage olimeric matrix protein, metalloproteinase-3 and pro-inflammatory cytokines (TNF-α, IL-1β and IL-17) was observed. Signal activation through janus kinases and mitogen-activated protein kinase was also drastically improved [105]. Fatty acids are the precursors of prostaglandins, thromboxanes and leukotrienes. There are numerous studies demonstrating that omega 3 supplements produce beneficial effects on the symptoms of RA [102]. Consumption of long-chain omega-3 polyunsaturated fatty acids, derived from fish and fish oil, is associated with a reduced risk of RA probably due to their anti-inflammatory properties [106]. Differently, excessive intake of omega-6 fatty acids may induce a proinflammatory state that may lead to inflammatory related disease [107]. High salt intake may play a role in the development of autoimmune diseases. In particular, high sodium intake appears to interfere with the suppressive effects of regulatory T cells (Tregs) and promote cellular displacement to the pro-inflammatory phenotypes T-helper (Th) -1 and Th17 [108,109]. In vitro, innate and adaptive immunity cells show an inflammatory profile when placed in hypertonic saline. In particular, macrophages release large quantities of pro-inflammatory cytokines and, by producing reactive oxygen species [ROS], activate the inflammasome [110]. Exposure of cells to hyperosmotic conditions causes numerous cellular stress events that could potentially activate the inflammasome formation, for example, cytoskeletal rearrangement due to cell shrinkage, solute influx (e.g. ions, water), and ROS production [111]. Excessive salt intake is associated with a higher risk of developing RA, particularly in smokers [110,112]. Sodium excess reduces the activation of innate non-inflammatory immune cells and can alter the mechanisms of regulation of the innate and adaptive immune system and expand the CD14 + CD16 + monocytes, leading to a general imbalance in immune homeostasis [113]. In RA patients, a trend towards a reduction in the frequencies of Th17 cells over the low-sodium dietary regimen was observed, while Treg cells exhibited the opposite trend [114]. Caffeine is part of the methylxanthine family of drugs and is an active substance on immune function by modulating innate and adaptive immune responses [115]. Caffeine and its major metabolite paraxanthine suppress neutrophil and monocyte chemotaxis, and suppress the production of the pro-inflammatory cytokine TNF-α from human blood [115]. High doses of caffeine seem to have an immunosuppressive action reducing activity of macrophages, natural killer cells and inflammatory cytokines such as IL-2, IL-6 and TNF-α [116]. Dose-dependent validation experiments showed down-regulation at mRNA levels of key inflammation-related genes including STAT1, TNF, IFNγ, and PPARG [99]. In RA contradictory data have been provided on the association between caffeine consumption and RA risk [106,117] possibly due to confounding factors as smoking habit. A meta-analysis stratified by seropositivity indicated a significant association between coffee consumption and seropositive RA risk [118]. Cocoa is a potent antioxidant, rich in polyphenols, and influences the innate and adaptive immune response with stimulatory effects [119]. The effect of a cocoa diet on in vivo models of arthritis, such as adjuvant arthritis and collagen-induced arthritis, has been reported to be partially protective towards the synthesis of autoantibodies, to reduce oxidative stress and ROS production, to prevent decrease in T-reg serum levels, although it does not reduce significantly joint swelling [120,121,122]. Turmeric (*Curcuma longa*) is an herb belonging to ginger family with a long history of use as food and as anti-inflammatory treatment in traditional Chinese and Ayurvedic medicine [123]. However, the systemic bioavailability of curcumin is known to be poor [124]. Unlike ginger, turmeric and curcumin do not modulate COX-1 activity, but modify NF-κB signaling, pro-inflammatory cytokines such as interleukin production and phospholipase A2, COX-2, and 5-lipoxygenase activities [125]. Curcumin has various pharmacological activities and acts by inhibiting cell proliferation and down-regulating various factors, including nuclear factor kappa B, IL-1β and TNF-α [126]. In a rat-model of experimentally induced arthritis, a combination of ginger and turmeric rhizomes was superior to indomethacin regarding the ability to alleviate both joint histopathological changes, and the extra-articular manifestations, including systemic inflammation [127]. A systematic review and meta-analysis evaluated the scientific evidence supporting the efficacy of turmeric extract (1000 mg/day of curcumin) in the treatment of osteoarthritis. Results suggested that curcumin (about 1 g/day) might have similar effects as analgesic and improve joint function in comparison with the placebo group [125]. However, future studies of dose finding, safety and efficacy in RA need to be performed.

Cigarette smoke is the risk factor that has the unequivocal strong association with RA: it has been repeatedly shown to increase the risk of ACPA-positive RA [128]. The risk of developing anti-CCP antibodies appears to be related to the severity of the disease in genetically predisposed individuals with the shared HLA-DRB1 gene epitope [129]. The role of smoke on radiographic progression appears controversial: Finckh et al. showed that radiographic joint damage progressed at an equivalent rate in smokers and non-smokers. Furthermore, a significant trend was observed for reduced radiographic progression and generally more favorable functional scores among heavy smokers, suggesting that cigarette smoke does not accelerate RA disease progression [130]. A recent study for the identification of risk factors for rapid joint destruction in RA investigated the relationship between the characteristics of the RA patient and the subsequent rapid radiographic progression, concluding that history of smoking, presence of RF and/or ACPA, early erosions, high initial disease activity and active disease at one year, increase the risk of radiographic progression [131]. Recent studies have shown an influence of cigarette smoking on RA patients' response to anti-rheumatic drugs. Smokers taking anti-TNF-α have a reduced chance of achieving a moderate response according to the EULAR response criteria compared to non-smokers [132]. Likewise, an observational cohort study evaluated RA patients treated with rituximab: overall results do not support smoking as an important predictor of RTX response in patients with RA [133].

Physical activity is a crucial part of the co-adiuvant therapies used in the management of patients affected by RA [134,135]. Many clinical trials have emphasized an improvement in aerobic capacity and muscle strength after physical exercise programs in RA patients. Furthermore, physical activity seems to produce a shift in the Th1/Th2 balance to a decreased Th1 cell production [136] and to promote in muscles the release of IL-6, a myokine with an anti-inflammatory action [137]. A

Table 1
Ongoing Clinical trials exploring behavioral interventions on Rheumatoid Arthritis.

Title	Type and model	Intervention	Primary outcome measures	Tools to assess primary outcomes	Identifier
Ultrasound Assessment of Rheumatoid Arthritis Patients Who Changed Diet	Interventional RCT Parallel Assignment	Dietary Supplement. Dietary counseling and recommendations	Synovitis; Disease Activity	Power doppler ultrasound; DAS28	NCT02881307
A Nutrition Intervention for Arthritis-3	Interventional Crossover Assignment	Low-fat, vegan diet, nutritional supplement	Pain Score; Disease Activity; Improvement in mood	Visual Analog Scale; number of painful swollen and tender joints; Beck Depression Inventory II	NCT03417648
REU-stop - Effect of Intensive Smoking Cessation Intervention on Smoking Cessation and Disease Activity in Patients With Rheumatoid Arthritis	Interventional RCT Parallel Assignment	Intensive smoking cessation intervention	Smoking cessation; EULAR clinical response	self-reported smoking cessation and exhaled carbon monoxide; DAS28	NCT02901886
Effect of Smoking on Pain and Atherosclerosis in Patients With Rheumatoid Arthritis	Observational Cohort Prospective	Outcome measures in smokers, former smokers and no smokers	Disease activity; Pain sensitivity; Pain perception; Cardiovascular risk	DAS28; pressure pain detection threshold; visual analogue scale; Framingham score	NCT03449589
Inflammatory and Vascular Response to Dietary Salt in Rheumatoid Arthritis	Interventional Crossover Assignment	High salt or low salt diet	Change in tissue sodium	Magnetic Resonance Imaging	NCT03649178
The Effects of a 12-week Cardiovascular Rehabilitation Exercise Program on Inflammatory Markers and Traditional Coronary Artery Disease Risk Factors in Patients With Rheumatoid Arthritis	Interventional RCT Parallel Assignment	Exercise (cardiac rehabilitation programs)	Cardiovascular risk; systemic inflammation; RA severity	Framingham risk score; serum levels of cytokines; ACR response score	NCT01534871
Reducing Sedentary Time in Rheumatoid Arthritis: The Take a STAND for Health Study	Interventional RCT Parallel Assignment	Personalized intervention with light- (or very light-) intensity physical activity	Sedentary time	Sedentary behaviour assessment	NCT03186924
Impact of Yoga on Quality of Life and Markers of Inflammation in Rheumatoid Arthritis Patients	Interventional RCT Parallel Assignment	Yoga program; arthritis-education	Health-related quality of life	Medical Outcomes Survey 36-item Short-Form Healthy Survey	NCT03500276
Empowering Active Self-management of Arthritis: Raising the Bar With OPERAS	Interventional RCT Crossover Assignment	Education, physical activity tracker and physiotherapist counseling	Self-management ability	Self-reported measure	NCT03404245

RA: Rheumatoid Arthritis; RCT: randomized controlled trial; DAS28: disease activity score on 28 joints; EULAR: European League Against Rheumatism; ACR: American college of Rheumatology.

recent meta-analysis conducted by Baillet and collaborators analized 40 Randomized controlled trials, including 1.040 patients with a diagnosis of RA, evidenced how cardiorespiratory aerobic conditioning exercise could improve the quality of life and disability, preserving a global safety and good compliance [138]. Moreover, physical exercise in autoimmune diseases due to anti-inflammatory mechanisms, decreases the cardiovascular risk in patients with RA, whereas bone mineral density and joints mobility improve [139]. All the aspects described can result in a reduction of disease flares and chronic use of NSAIDs, a minor incidence of cardiovascular accidents and other comorbidities, and an easier management of drug therapy [140]. Despite all the evidences collected from these studies, there are few recommendations concerning type, frequency and duration of physical exercise in these patients. EULAR recommendations published in 2018 for physicians concerning physical activity in inflammatory arthritis [141] suggest to introduce physical exercise as co-adiuvant medication in RA patients and refer to the American College of Sports Medicine and American Heart Association primary physical activity recommendations, without taking into account difficulties which can be faced by patients with arthritis in the execution of different kind of exercise. Moreover, EULAR recommendations published in 2018 for health professional's regarding the management of pain in patients with arthritis [142] highlight the value of introducing aerobic exercise, strength and resistance training to improve quality of life of patients, however without examining the topic in a more detailed way. It is clear that a more specific and routed protocol of physical activity is required in the handling of these patients. Clinical trials on behavioral targets in RA are mandatory to explore their role in the management of RA (Table 1).

Competing interests

The authors declare they have no competing interests.

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