Expert Opinion

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Efalizumab

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Introduction: Conventional systemic therapies for psoriasis are associated with serious toxicities that can limit long-term use. In recent years, biological therapies have offered the possibility of long-term therapy with improved safety and efficacy for the treatment of psoriasis. Biological therapies can be classified into three categories: the T-cell modulating agents (alefacept and efalizumab), the inhibitors of TNF-α (adalimumab, etanercept, infliximab) and the inhibitors of IL-12 and -23 (ustekinumab). Efalizumab is a humanized recombinant monoclonal IgG1 antibody. It targets multiple stages in the immunopathogenesis of psoriasis: initial T-cell activation, migration of T-cells into dermal and epidermal tissues, and T-cell reactivation. On 19 February 2009, the Committee for Medicinal Products for Human Use (CHMP) recommended the suspension of the marketing authorisation for efalizumab.

Areas covered: Numerous clinical trials have demonstrated the efficacy, safety and health-related quality of life benefits of efalizumab in patients with moderate-to-severe chronic plaque psoriasis. Efalizumab was approved by the FDA in November 2003 and by the European Medicines Evaluation Agency in September 2004 for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis. Recently, three cases of progressive multifocal leukoencephalopathy were described in patients on long-term (> 3 years) efalizumab therapy, leading to its withdrawal from the market.

Expert opinion: Although initially favorable, the safety profile of efalizumab revealed the appearance of severe adverse events in long-term treated patients. Therefore, post-marketing surveillance is essential for correct evaluation of drug potential.

Keywords: biologics, efalizumab, psoriasis, safety

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1. Introduction

Psoriasis is a chronic inflammatory systemic disease affecting between 1 and 3% of the population in Europe and the US [1,2].

Traditional systemic therapies for psoriasis such as methotrexate, cyclosporin A, retinoids or psoralen UVA (PUVA) therapy have a potential for long-term toxicity and may not always provide sufficient improvement of the disease. New targeted biologic therapies have been developed in response to this unmet need through an increased understanding of the immunopathological basis for psoriasis.

Biological therapies for the treatment of psoriasis can be classified into three categories: the T-cell modulating agents (alefacept and efalizumab), the inhibitors of TNF-α (TNF-α blockers, e.g., adalimumab, etanercept, infliximab) and the inhibitors of IL-12 and -23 (e.g., ustekinumab and briakinumab).

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Article highlights.

- Efalizumab was the first plaque psoriasis-specific biologic drug.
- This drug has shown a long term favorable efficacy in about two-thirds of patients.
- Drug-related adverse events were generally mild and consisted of infections and psoriasis eruptions.
- The occurrence of three cases of progressive multifocal leukoencephalopathy in long term-treated patients led to the withdrawal of efalizumab from the market.

This box summarizes key points contained in the article.

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Efalizumab (Raptiva™, Genentech, South San Francisco, CA, USA), a recombinant humanized monoclonal IgG1 antibody directed against *a* subunit (CD11a) of leukocyte function-associated antigen-1 (LFA-1) blocks LFA-1-mediated T-cell adhesion.

In Phase I and II trials, the pharmacokinetic and pharmacodynamic effects of efalizumab were determined in psoriasis patients. Single or multiple doses of efalizumab by intravenous or subcutaneous (s.c.) routes resulted in rapid saturation of available cell surface CD11a binding sites on T cells and downregulation of CD11a expression on T lymphocytes in the dermis, epidermis and in the circulation. These effects were reversible and once efalizumab was cleared from the circulation, CD11a binding sites return to pretreatment levels within 10 days [3,4].

In binding to CD11a, efalizumab inhibits the interaction of LFA-1 with intercellular adhesion molecule-1 (ICAM-1), and thus blocks multiple key T-cell-mediated events involved in the immunopathogenesis of psoriasis, including T-cell activation by the antigen-presenting cell, T-cell adhesion and trafficking from the circulation into psoriatic lesions, and T-cell reactivation in psoriatic skin.

Efalizumab is self administered as an s.c. injection as an initial single 0.7 mg/kg body weight dose followed by weekly injections of 1 mg/kg body weight [5,6].

Efalizumab was approved by the FDA in November 2003 and by the European Medicines Evaluation Agency in September 2004 based on studies in ~ 2700 patients, of whom only 218 were exposed to the drug for > 1 year.

It is approved for the treatment of adult patients (aged ≥ 18 years) with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (in the US) or who have failed to respond to, have a contraindication to or are intolerant of other systemic therapies, including cyclosporine (ciclosporin), methotrexate and PUVA photochemotherapy (in the EU).

In addition to psoriasis, there are many other conditions that have been presumably successfully treated with this agent, including pustular psoriasis of the palms and soles, generalized granuloma annulare [7], cutaneous lupus erythematosus [8], cutaneous dermatomyositis [9], atopic dermatitis [10] and alopecia areata [11].

Besides the Phase I and II trial experience, numerous Phase III clinical trials including four large placebo-controlled and one 3-year, open-label trial have demonstrated the efficacy, safety and health-related quality of life benefits of efalizumab in patients with moderate-to-severe chronic plaque psoriasis.

Collectively, these trials characterize the response of patients to short-term (12 weeks), intermediate-term (24 weeks) and long-term (36 months) efalizumab therapy [12-17].

A post-approval open-label trial (study acronym CONTROL II IMP25300) evaluated the efficacy and safety of efalizumab in the restricted, difficult-to-treat, European-label and the management of psoriasis rebound and exacerbation during or after efalizumab treatment [18].

After a single s.c. conditioning dose of efalizumab 0.7 mg/kg, eligible patients received open-label s.c. efalizumab at a dose of 1 mg/kg once a week for a further 11 weeks, and patients were classified at week 12 according to the dynamic Physician Global Assessment (PGA) rating as responders ('good', 'excellent' or 'cleared') or non-responders.

Responders could continue to receive weekly open-label s.c. efalizumab at 1 mg/kg for up to 8 weeks and non-responders transitioned to alternative anti-psoriasis medication or stopped treatment.

Between 13 December 2004 and 12 April 2006, 1266 patients were enrolled in the trial and a total of 688 patients continued into the efalizumab continuous treatment period after week 12 (**Figure 1**).

Among those patients, 79.5% had a PGA rating of 'good', 'excellent' or 'cleared' at week 20.

Psoriasis Area and Severity Index (PASI) by week 12, the median improvement from baseline in PASI score in the intent-to-treat (ITT) population, was 68.4% (median PASI score at baseline of 19.55 and 6 at week 12). The proportion of patients in the ITT population with a PASI 50/PASI 75/PASI 90 response increased throughout the first treatment period to 65.5/35.9/13% at week 12. At week 20, the median PASI score was 3.90 for patients in the continuous treatment period and the proportion of patients in the ITT population with a PASI 50/PASI 75/PASI 90 response increased further through the continuous treatment period to 78.2/52.9/24.3% of responders at week 20 (**Figure 2**).

Of the 127 responders at week 12 who discontinued efalizumab, 11% experienced rebound and 56.7% relapsed with a median time to relapse of 56 days and this appears similar to that observed with methotrexate and cyclosporine [19-23]. Adverse events are summarized in **Table 1**.

Interestingly, recent data identified genetic markers as a potential predictor of response to efalizumab.

The presence of the histocompatibility antigen HLA-Cw6 has been associated with the presence of psoriasis and appears to confer a risk for more severe disease as well as early-onset psoriasis. Recently, other data suggest that the HLA-Cw6 polymorphism may also be capable of predicting response to some therapies. A study by Gulliver [24] demonstrated that

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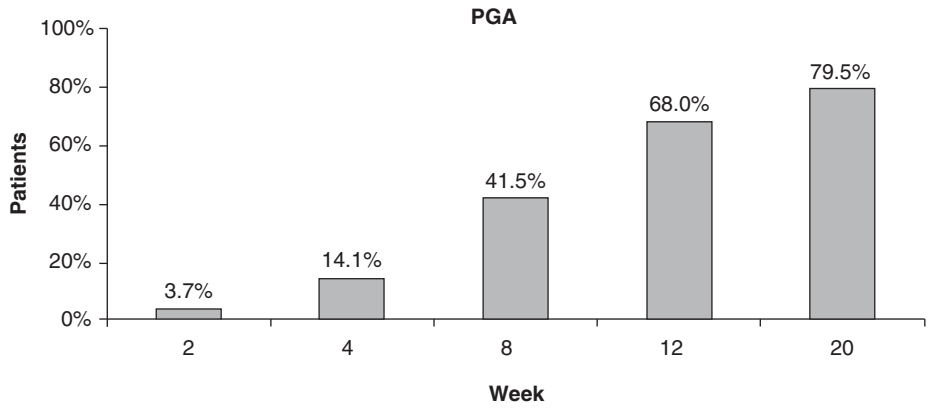

Figure 1. Proportions of efalizumab patients with a PGA rating of 'good', 'excellent' or 'cleared' by visits at weeks 12 and 20.
PGA: Physician Global Assessment.

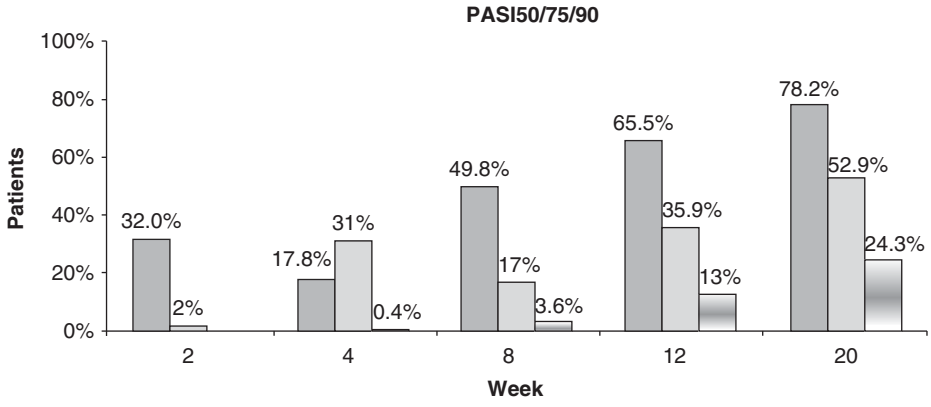

Figure 2. Proportions of patients with PASI 50, PASI 75 and PASI 90 responses.
PASI: Psoriasis Area and Severity Index.

the presence of the HLA-Cw6 allele was predictive of a response to treatment with efalizumab: all patients possessing the allele (N = 11) responded to treatment with efalizumab, compared to only 50% of patients without the allele who responded to treatment (p = 0.012). Costanzo *et al.* [25,26] reproduced this finding, demonstrating that 81.8 and 34.7% of patients testing positive for the HLA-Cw6 allele achieved a 50 and 75% improvement in PASI scores (i.e., PASI 50 and PASI 75), respectively, after 12 weeks of efalizumab therapy. Of patients who lacked the allele, only 58.3% achieved PASI 50 and 16.7% achieved PASI 75. Interestingly, presence of the allele was not predictive of a response to anti-TNF-α therapy, such as etanercept.

The efficacy of efalizumab has been demonstrated both in clinical trials and in several years of off-trial experience. An important advantage of efalizumab over other biologic drugs was the stability and maintenance of clinical response over time. Also, in recent years, there have been several cases of successful use of efalizumab in patients with a history of heart failure [27] and in patients with difficult to treat psoriasis co-morbidities such as cardiovascular disease, metabolic syndrome and liver diseases [28].

The same results cannot apparently be obtained with TNF blocker biologics, which are contraindicated in most of the morbidities associated with psoriasis [29-31].

2. Acute adverse events

Efalizumab was generally well tolerated with similar incidence and type of adverse events in previous Phase III clinical trials.

The data from clinical trials indicate that the most common side effect is an flu-like syndrome that may include headaches, chills, fever, nausea and myalgia, which usually occur within 48 h following the first two injections, are dose-dependent and usually well tolerated at the dose of 0.7 mg/kg [32]. The incidence of such symptoms after the first injection was 27.4% in the group receiving efalizumab as compared with 21.2% in the placebo-treated group.

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Table 1. AE summary of the safety population during efalizumab treatment.

	Numbers of patients (%)	
	FT period (N = 1266)	CT period (N = 688)
Any AE	785 (62)	122 (17.7)
Serious AE	60 (4.79)	10 (1.5)
AE leading to withdrawal	89 (7)	4 (0.6)
Nervous system disorders	355 (28)	9 (1.3)
General disorders and administration-site conditions	318 (25.1)	10 (1.5)
Infections and infestations	212 (16.7)	35 (5.1)
Musculoskeletal and connective tissue disorders	176 (13.9)	21 (3.1)
Skin and subcutaneous tissue disorders	170 (13.4)	32 (4.7)
Gastrointestinal disorders	138 (10.9)	7 (1)
Malignancy	4 (0.3)	0 (0)
Death	1 (0.1)	0 (0)

AE: Adverse event; CT: Continuous treatment; FT: First treatment.

Paracetamol or ibuprofen is suggested in case of such events or as premedication [33]. In particular, headaches are the most common of these side effects, affecting 32% of patients in clinical trials. The frequency of such symptoms decreased markedly when the treatment was continued for three or more injections (3.7% in the efalizumab group vs 3.9% in the placebo group).

Efalizumab was generally well tolerated during the 36 months of continuous treatment. There was no increase over time in the overall incidence of adverse events, no increase in common adverse events, no emergence of new adverse events, no apparent trend towards an increase in the incidence of clinically significant adverse events, and no evidence of cumulative or end-organ toxicity.

Psoriasis adverse events were generally mild or moderate in severity.

Hamilton analyzed > 3500 patients with psoriasis who have been treated in 14 efalizumab clinical trials [34]. Importantly, some of these patients have participated in the longest running trial in psoriasis patients with any biologic agent: a recently completed, 36-month, open-label Phase III trial (ACD2243g). Efalizumab clinical trials have provided investigators substantial experience with efalizumab in patients with moderate-to-severe psoriasis. As psoriasis fluctuates in severity, the response to treatment with efalizumab or other psoriasis therapies can vary widely among patients. Hamilton assessed that 60 – 70% of his patients experienced excellent improvement, achieving a static PGA and observed that the potential for variability in response to efalizumab therapy is most evident within the first 3 months after initiation, after which most patients enter a period of continuous long-term psoriasis control. During this early treatment window, patients generally respond in one of three ways: i) patients respond well to efalizumab without the occurrence of an intercurrent psoriasis event, ii) the original psoriasis plaques respond well to therapy but patients develop a transient psoriasis papular eruption or mild arthropathy during therapy or iii) patients experience a generalized form of inflammatory psoriasis instead of showing improvement or develop a significant inflammatory arthropathy irrespective of the response in the skin. As intercurrent psoriasis events generally present within the first 3 months of initiating efalizumab therapy, patients should be more closely monitored during this time. After this time, most of responding patients demonstrate continuous long-term disease control. Soon after treatment initiation, it is not always clear whether a patient will respond to therapy. Some patients who respond to efalizumab may develop a transient localized papular eruption or mild arthropathy. Although infrequent, some patients, generally those who do not respond to efalizumab, may develop a generalized inflammatory flare or arthropathy.

Many patients who experience an intercurrent psoriasis event wish to remain on efalizumab therapy or be retreated with efalizumab after discontinuation because of improvements in their psoriasis. These patients demonstrate that the long-term benefits of efalizumab therapy outweigh the occasional short-term challenge. The temporary addition of concomitant medications early in therapy and proper patient education about the long-term durability once response is attained will result in effective utilization of efalizumab in the dermatology community [35].

Exacerbation of psoriasis including erythrodermic, guttate or pustular forms (2.2% in the efalizumab-treated group vs 0.8% in the placebo group) as well as worsening of psoriatic arthritis (1.6% in the efalizumab-treated group vs 1.3% in the placebo group) may be observed during treatment with efalizumab [36].

The most severe of these events is the so-called generalized inflammatory flare that has been defined as the development of a flare of inflammatory. In the first 12-week period of placebo-controlled trials, psoriasis adverse events occurred in 3.2% of efalizumab-treated patients compared with 1.4% in the placebo group and were predominantly mild to moderate in severity. This event typically presents as widespread, erythematous, edematous lesions and involves existing plaques. Generalized inflammatory flares are typically observed in patients who do not respond to efalizumab therapy and most often occur in the first 6 – 10 weeks after initiating efalizumab and in some cases can be solved by adding a short course of classic psoriasis systemic therapy to the biologic agent.

After discontinuation of efalizumab, a significant proportion of patients may experience rebound (defined as PASI 125% of baseline or newly developing pustular or erythrodermic psoriasis occurring within 8 weeks of discontinuation). The incidence of rebound (as defined in the efalizumab analyses) during the 12 weeks after efalizumab discontinuation in multiple clinical trials was 14%. Less than 1% (0.7%)

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of patients experienced a serious psoriasis adverse event or a severe adverse event of erythrodermic, pustular or more inflammatory psoriasis after discontinuation of efalizumab. Plans for management of flares or a change in character of the disease should be made at the onset of therapy. Physicians unwilling to use other systemic agents such as methotrexate, acitretin or cyclosporin for patients whose disease flares with efalizumab should perhaps reconsider the use of this agent [36,37].

Transient papular eruptions are rashes that consist of localized papules and plaques that typically appear during the first 4 – 8 weeks of efalizumab therapy and frequently present on the neck, torso and flexural areas, although any body site can be affected. This reaction has been explained by the alternative use of surface markers for T-cell trafficking. Histologically, they represent inflammatory psoriatic plaques and discontinuation of efalizumab is usually not required in these cases and papules typically clear with continued efalizumab therapy. Adding a concomitant topical therapy to efalizumab can help establish control of the eruption [38,39].

Worsening or *de novo* psoriatic arthritis during or following efalizumab therapy has also been reported [40].

In the published European 'CLinical Experience Acquired with Raptiva' (CLEAR) study, arthralgia was reported in 7.4% of the patients treated with efalizumab (compared to 3% of those receiving placebo) [41].

Bang and Gniadecki [42] suggested that this phenomenon could be explained by the mechanism of action of the drug, which impairs T-lymphocyte trafficking to sites of cutaneous inflammation. Thus, T cells would be redistributed and increased in other compartments such as the joints, provoking the articular response. A previous history of arthropathy and poor clinical response seem to increase the possibility of developing articular symptoms [43]. There was, however, no increased incidence of arthropathy in efalizumab-treated patients in a long-term study for up to 3 years [44].

Martin *et al.* [45] presented six cases in which an inflammatory flare appeared in a delayed fashion between 23 and 72 weeks after the therapy was started. All six patients had, until then, been responding to the treatment, with a dramatic improvement of their psoriasis with efalizumab. These two characteristics make this event distinctive and different from what has previously been reported. The pronounced worsening of the cutaneous psoriatic lesions was accompanied by severe musculoskeletal involvement in all cases. All of them had chronic, stable moderate-to-severe plaque psoriasis and had undergone other systemic therapies before efalizumab. The PASI scores when efalizumab treatment was started ranged from 9 to 20.1 (mean 15.1). The flare started between weeks 23 and 72 and in all cases arthalgia was also observed. In one of these patients, scintigraphy showed increased uptake in the joints. After discontinuation of efalizumab, none of the patients experienced another episode of arthritis during 18 months of follow-up.

Relatively uncommon adverse events included urticaria, rashes and other presumably allergic reactions.

Antibodies directed against efalizumab were detected in 2 – 6% of patients, apparently without clinical relevance [46,47].

3. Hematologic adverse events

Serious adverse effects are rare and include thrombocytopenia, hemolytic anemia and infections.

Lymphocytosis (which is sustained during efalizumab treatment) can be observed in up to 40% of patients and is presumably because of the specific mode of action of the compound [47].

Thrombocytopenia (b 52,000 platelets/ml), which again resolved after discontinuation of efalizumab, was observed in 0.3% of patients in the clinical trials. Significant efalizumab-associated thrombocytopenia has been documented as causing petechiae, purpura and bleeding from mucosal membranes.

The initial clinical development trial for efalizumab involved 2762 patients treated for a minimum of 12 weeks [48]. Platelet count was at or below 52×10^9 cells/l. Eight (0.3%) patients developed thrombocytopenia during treatment. Warkentin and Kwon [49] reviewed all eight cases and determined that two were unrelated to efalizumab (one patient had metastatic prostate cancer; one had chronic thrombocytopenia before efalizumab treatment).

Mapping of the serial platelet counts for each patient showed that the onset of thrombocytopenia occurred after 8 – 12 weeks of therapy in 5 of 6 patients. The sixth patient had been taking efalizumab for longer than 1 year and developed thrombocytopenia 2 months after valproic acid was added to the treatment plan.

After efalizumab was discontinued, the thrombocytopenia resolved in 1 – 9 weeks in all patients. Their review indicated that the majority of patients with efalizumab-associated thrombocytopenia will manifest in the first 12 weeks of treatment; thus, the recommendation was to monitor the platelet count monthly for the first 3 months, then every 3 months for the remainder of therapy.

However, the case report from Hostetler *et al.* [50] and two prospective studies have documented late-onset thrombocytopenia associated with extended efalizumab therapy and they highlight the need for further laboratory evaluation during treatment. Prospective studies of extended efalizumab therapy, however, indicate that thrombocytopenia may occur with a later onset. Using a randomized, placebo-controlled design, Gottlieb *et al.* [51] followed up 339 patients through 27 months of efalizumab therapy. They reported a mild decrease in the average platelet count over time, from 265×10^9 cells/l before therapy to 235×10^9 cells/l at month 27. In any 3-month window during the study, an average of 11 (3.2%) patients were thrombocytopenic on routine monitoring. Furthermore, a total of four patients had five mild-to-severe episodes of symptomatic thrombocytopenia during the 27 months. Episodes occurred after 21 months of efalizumab

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therapy. The thrombocytopenia resolved spontaneously after discontinuation of efalizumab for every patient in this study and no patient required corticosteroids.

The substantially increased incidence of thrombocytopenia in this study compared with the clinical trial (3.2 vs 0.22 – 0.3%) is probably related to the more inclusive definition of thrombocytopenia used in this study (130×10^9 cells/l vs 52×10^9 cells/l).

Another randomized, placebo-controlled study followed 498 patients through 24 weeks of efalizumab therapy [52]. Researchers reported one case of thrombocytopenia that occurred after 16 weeks of efalizumab therapy. This patient had a nadir of 52×10^9 cells/l and recovered fully with discontinuation of efalizumab and a short course of corticosteroids.

Unfortunately, other studies of extended efalizumab therapy have not reported the incidence or timing of thrombocytopenia. Additionally, no study reporting thrombocytopenia documented whether these patients had a different likelihood of responding to efalizumab clinically compared with patients without significant adverse events [52-54]. This case prompted us to review the data on efalizumab-associated thrombocytopenia. Although the data are sparse, this case report and several prospective trials suggest that the highest risk period for onset of efalizumab-associated thrombocytopenia is 8 – 16 weeks after therapy is initiated.

The most likely mechanism of thrombocytopenia is a drug-induced autoantibody against a component of the platelet membrane, although such antibody(ies) have not been specifically demonstrated in any case of efalizumab-induced thrombocytopenia.

The mechanism for the hematological toxicity is not clear, but it is advised that patients be monitored monthly during the first 3 months of therapy. This recommendation is based on the initial clinical trial for efalizumab that indicated most episodes of thrombocytopenia occurred in the first 12 weeks of therapy [55].

Four cases of hemolytic anemia have been reported with efalizumab. Two cases were reported during clinical trials and occurred between 4 and 6 months after initiation of therapy. These cases were associated with a decrease in hemoglobin level to 6 and 7 g dl, requiring discontinuation of therapy and transfusion.

The other two cases of hemolytic anemia occurred post-marketing and little information is available on these cases [56,57].

Tom *et al.* also reported the first case of efalizumab-associated immune-mediated pancytopenia [58].

The case represents the first known reported case of efalizumab-associated pancytopenia. Noticeably, the findings were consistent with an immune-mediated mechanism causing pancytopenia, with hemolysis in the presence of a red-cell autoantibody, neutropenia and thrombocytopenia with adequate marrow megakaryocytes but refractory to platelet transfusions. The hemolysis may have been amplified by an inadequate marrow response, resulting in significant anemia. The prompt response of the patient's thrombocytopenia to immunomodulation (IVIG and prednisone) was also consistent with an immune-mediated process.

The exact role of efalizumab in the development of autoimmune pancytopenia is not clear. Drug-induced autoantibodies may recognize combinatorial epitopes formed by drug binding to a membrane glycoprotein (example: quinine) or a conformational change in a glycoprotein induced by drug binding at a different cell membrane site (example: tirofiban). Some drugs, such as gold salts, may perturb the immune response such that autoantibodies to a glycoprotein are generated without the need for simultaneous drug binding (drug-independent antibodies) [59].

A case of autoimmune agranulocytosis with granulocyte-bound and neutrophil specific-bound antibodies has been reported with infusion of infliximab. Infliximab is a chimeric (human and murine) mAb that binds to and blocks the effects of TNF-α. Cytopenia has also been reported with other TNF-α blockers, but it is unclear whether this is secondary to the immunogenicity of the molecules themselves or secondary to TNF-α blockade as this cytokine affects hematopoietic stem cell differentiation [60,61]. In the case of efalizumab, a direct drug effect is unlikely. CD11a is found not only on lymphocytes but also on neutrophils and activated platelets [57-62]. However, given its absence on mature erythrocytes, antibodies recognizing efalizumab binding to CD11a would not fully explain the pancytopenia in this case. Induction of drug-independent autoantibodies that affected all three cell lines appears to be a more plausible mechanism.

4. The risk of tumor and infections

Given that serious infections or the risk of tumor development are general concerns with immunomodulating therapies, these parameters have been extensively studied in efalizumab-treated patients.

In a pooled analysis of multiple Phase III open-label and placebo-controlled clinical trials, it was found that efalizumab by itself does not increase a patient's risk for malignancy [63,64].

However, the incidence of non-melanoma skin cancer, including basal cell and squamous cell carcinomas, seems to be slightly elevated in efalizumab recipients with signs of sun damage and/or history of PUVA treatment [65,66].

In a review of malignancies observed with efalizumab, Leonardi *et al.* [63] pooled patient data from 14 Phase III placebo-controlled, open-label clinical trials involving 2980 patients treated with efalizumab. In patients treated with efalizumab, three cases of LPD were reported in 2558 patient-years of follow-up, yielding an incidence rate of 0.12/100 patient-years.

Only a few isolated case reports have been documented reporting the association of efalizumab with lymphomas [67-69].

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Because many therapies for psoriasis disrupt the normal inflammatory cascade and could theoretically impair the body's ability to respond to external pathogens, a possible increase in the incidence of infection is a concern with any new psoriasis therapy that affects the immune system. Immunologic events are pivotal in the initiation of psoriasis and required for the continued expression of psoriasis symptoms [70,71]. Specifically, aberrant interactions between activated T cells and keratinocytes result in the keratinocyte proliferation and differentiation characteristic of psoriasis. A literature search using MEDLINE (key terms: psoriasis, infection, risk and rate; years: 1995 – 2005) revealed that little research is available concerning the underlying risk for infection in patients with psoriasis. However, it is known that with immunosuppression, there is potential for new-onset infections or reactivation of latent infections, and opportunistic infections are of concern when any immunosuppressive therapy is administered.

For example, studies have shown that cyclosporine can be associated with influenza-like symptoms (9.9%) and upper respiratory tract infections (7.7%) when administered to patients with psoriasis. It has also been found that methotrexate might cause leukopenia that could reduce resistance to infection [72]. An important advance in the management of psoriasis has been the development of targeted biologic therapies made possible by an improved knowledge of the pathogenesis of psoriasis. Still, biologic agents are immunosuppressants that target cytokines or specific immune cell subpopulations. The long-term safety profiles of biologic therapies are being assessed in patients with psoriasis. There remains a concern that, as with any immunosuppressant, biologic therapies might reduce resistance to infection. For example, TNF-α is important in host defense against infection [73,74] and inhibitors of this cytokine have been associated with cases of tuberculosis (TB) reactivation. Likewise, T cells are crucial to the immune response [75]; thus, their reduction or inhibition could theoretically increase the risk for infection.

Efalizumab reversibly blocks LFA-1 and is not associated with lymphocyte depletion. In clinical studies, a trend toward increased mean circulating lymphocyte counts was shown during efalizumab therapy, but the counts remained within normal ranges. The elevation was most likely due to the inhibition of T-cell trafficking from the circulation into inflamed skin. Leukocyte counts returned to baseline after efalizumab discontinuation [76-79].

Because efalizumab, like all biologic therapies for psoriasis, alters the normal inflammatory cascade and could, therefore, impair the body's ability to respond to external pathogens, it was important to assess the incidence of infection in patients receiving efalizumab therapy in the clinical trials.

During the first 12 weeks of treatment, the overall incidence of infection in the efalizumab-treated group was statistically similar to that of the placebo group (28.6 vs 26.3%). The majority of infections were considered mild-to-moderate in intensity. Serious infections requiring hospitalization occurred infrequently during the efalizumab trials. Of 2475 efalizumab-treated patients, 27 (1.1%) were hospitalized because of infection. During controlled trials, 2 of 715 (0.3%) patients receiving placebo were hospitalized because of serious infection; one of the two events occurred during the post treatment follow-up period.

No clear correlation was found between efalizumab treatment and any particular type of infection requiring hospitalization. The serious infections resolved in 26 of 27 (96.3%) efalizumab-treated patients, with 1 patient being lost to follow-up. In all, 10 of 2475 (0.4%) efalizumab-treated patients discontinued treatment because of a serious infection requiring hospitalization.

Serious infections requiring hospitalization included cellulitis, pneumonia, abscess, sepsis, bronchitis, gastroenteritis, aseptic meningitis, Legionnaire's disease and vertebral osteomyelitis.

During the efalizumab clinical trials, no clear increase was found in the frequency or severity in the types of infection commonly observed in immunocompromised individuals, including HSV and HZV infection or reactivation [79]. No evidence of systemic dissemination, as might be observed in immunosuppressed hosts, was found.

Long-term treatment appeared to effect no increase in the risk for infection (**Table 2**) [80].

Based on all clinical data available thus far, it appears that both the risk of increased infection rates and the development of malignant tumors are similar in patients with psoriasis treated with efalizumab and the general population of patients with psoriasis.

In particular, in clinical trials, there was no increased risk for opportunistic infections (including TB) during treatment periods of up to 3 years. However, the use of clinical trial data can be limited by ascertainment bias, use of homogeneous populations, limited co-morbid diseases, small numbers of patients and short trial duration. In addition, patients with a history of or ongoing uncontrolled bacterial, viral, fungal or atypical mycobacterial infection; a history of opportunistic infections (e.g., systemic fungal infections, parasites) or a history of active TB; patients who were undergoing treatment for TB; and patients with seropositivity for HBV and HCV or HIV were excluded from the clinical trials [80,81].

However, opportunistic infections have been reported in the post-marketing surveillance in patients with psoriasis receiving efalizumab. Four cases of efalizumab-induced aseptic meningitis have been reported: two cases were mentioned in a review of events reported during clinical trials [82] and two cases were reported by Kluger *et al.* [83] and Rivas-Rodríguez *et al.* [84].

Kluger *et al.* [83] reported the first detailed case of aseptic meningitis induced by efalizumab. Forty-eight hours after the injection of efalizumab day at a dose of 0.7 mg/kg, a 32-year-old patient with a 14-year medical history of severe psoriasis experienced severe headaches of increasing intensity, later complicated by photophobia, phonophobia

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Table 2. Incidence of infection during efalizumab therapy for psoriasis: analysis of the clinical trial experience.

	Controlled trials (weeks 1 – 12)		Extended treatment		
	Efalizumab (N = 1620)	Placebo (N = 715)	Weeks 1 – 12 (N = 1713)	Weeks 13 – 24 (N = 1115)	≥ 12 Weeks (N = 1166)
Serious infection, % (95% CI)	0.4 (0.2 – 0.9)	0.1 (0 – 0.8)	0.4 (0.2 – 0.8)	0.3 (0.1 – 0.8)	0.7 (0.3 – 1.3)
Diagnosed infection-related					
AEs leading to withdrawal % (95% CI)	0.4 (0.2 – 0.9)	0.4 (0.1 – 1.2)	0.5 (0.2 – 0.9)	0.4 (0.1 – 1)	NR
All diagnosed infection-related AEs (95% CI)	28.6 (26.4 – 30.9)	26.3 (23.1 – 29.7)	28.9 (26.8 – 31.1)	27.3 (24.7 – 30)	20.9 (18.6 – 23.4)
Diagnosed infection %					
Nonspecific infection	13.9	15.4	14.5	15	11.8
HSV	4.6	3.4	4.6	3.4	1.9
Gastroenteritis	2.1	3.4	1.3	1.6	0
Infection viral	1.9	1.1	1.8	0.7	0.7
Bronchitis	1.7	1.3	1.8	2	2.2
Urinary tract infection	1.4	1.3	1.8	1.7	1.2
Otitis media	1.4	1.3	1.6	2	1.4
Infection, bacterial	1.2	0.6	1.1	0.8	0.7
Fungal dermatitis	0.9	0.1	1.1	1	0.4
Cellulitis	0.8	0.4	1.1	0.4	0.3
Periodontal abscess	0.6	0.3	0.5	0.4	0.3
Infection, fungal	0.4	0	0.6	0.4	0.5
Pneumonia	0.4	0.3	0.4	0.3	0.3
Furuncolosis	0.4	0.4	0.5	0.8	< 0.1
Abscess	0.2	0	0.3	0.2	0.2
HZV	0.2	0	0.2	0.5	0.2
Vaginalis moniliasis	0.2	0.1	< 0.1	< 0.1	0.3
Infection, parasitic	0.1	0	0.1	0	< 0.1
Oral moniliasis	0.1	0	0.1	< 0.1	< 0.1
Hepatitis	< 0.1	0	0.1	< 0.1	-
Auxiliary moniliasis	< 0.1	0	< 0.1	0	
Sepsis	< 0.1	0	0	0	02.2
Meningitis	< 0.1	0	< 0.1	0	-
Moniliasis, unspecified	0	0.1	0	0	-
Peritonitis	0	0	0	0	< 0.1
Osteomyelitis	0	0	0	0	< 0.1
Pyelonephritis	0	0	0	< 0.1	0.2

HSV: Herpes simplex virus; HZV: Herpes zoster virus.

and neck stiffness. Neurological examination revealed nuchal rigidity. Except for widespread psoriasis lesions, no other skin eruption or reaction at the site of efalizumab injection was observed.

A diagnosis of efalizumab-induced aseptic meningitis was established. The arguments supporting a correlation between meningitis and efalizumab injection included: i) rapid development of symptoms within 48 h after the onset of treatment; ii) negative findings from extensive investigations for infectious agents; iii) absence of other causes of meningitis and iv) reversibility after discontinuation of the drug.

Drug-induced aseptic meningitis (DIAM) is an uncommon adverse reaction mainly caused by NSAIDs, antibiotics, intravenous immunoglobulins, mAbs (OKT3 antibodies, infliximab), intrathecal agents and vaccines. Of note, it appears that patients with autoimmune diseases are more susceptible to develop DIAM. The patient presented autoimmune hyperthyroidism, although this association might have been fortuitous.

The pathogenic mechanisms remain unknown, although an immunological type III or IV hypersensitivity is suspected when the drug has not been directly introduced into the CSF [85]. In the skin, efalizumab blocks the binding of LFA-1 to ICAM-1. In the CNS, ICAM-5 (telencephalin), expressed by neurones of the mammalian brain, is of major importance for leucocyte binding to neurones. ICAM-5 binds specifically to the leucocyte integrin CD11a/CD18 and antibodies against CD11a/CD18 can disrupt this interaction [86]. Thus, the aseptic meningitis could be a consequence of the blocking of LFA-1 and ICAM-5 interaction by efalizumab. Another mechanism might be that efalizumab binds to a crossreacting neural antigen, thereby, inciting local inflammation, as suspected by some authors for OKT3 antibodies [85].

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The physician should be alerted by unusually severe headaches. Efalizumab-induced meningitis may not be rare but simply under-recognized given that headaches commonly occur during this treatment.

One case of transverse myelitis was observed during the clinical development program (2762 efalizumab-treated patients) and neurologic events, including cases of Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, facial palsy and transverse myelitis, have been observed in patients receiving efalizumab in the post-marketing setting [87].

A recent case of visceral leishmaniasis infection has been reported underscoring that visceral leishmaniasis should be taken into account during efalizumab treatment, at least for patients living in endemic areas [88].

A disseminated eruptive giant molluscum contagiosum [89] and a case of CMV colitis [90] have been reported recently under efalizumab treatment too.

Opportunistic infections have been reported in the post-marketing surveillance in patients with psoriasis receiving efalizumab. In particular, cases of JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving efalizumab continuously for > 3 years.

PML, a usually fatal demyelinating disorder, results from infection with a ubiquitous polyoma virus and can occur in patients with severe immunosuppression. This polyoma virus was named JC virus by Padgett *et al.*, based on the initials of the patient from whom the virus was first isolated in 1971 [91-93].

The prevalence of PML in the general population was estimated at 4.4 cases/100,000 individuals, according to data from a medical service and out-patient prescription claims database [94]. In recent years, PML is reported in patients who have received mAbs including natalizumab for MS and Crohn's disease [95-97], rituximab for lupus [98] and efalizumab for psoriasis [99-100].

The mechanism of PML development after mAb treatment remains controversial, although for natalizumab and efalizumab, inhibition of T-lymphocyte trafficking into the CNS is thought to be responsible, at least in part.

On 19 February 2009, after > 46,000 patients were exposed to efalizumab, the Committee for Medicinal Products for Human Use issued an opinion recommending the suspension of the marketing authorization for efalizumab in all member states in which the product was marketed, as its benefits in the treatment of psoriasis were modest, while there was a risk of serious side effects. The recommendation was based on a re-evaluation of the benefit:risk ratio after the occurrence of three confirmed and one suspected case of PML.

The PML appeared in patients who were 47 – 73 years. Two of the patients with confirmed PML and one patient with possible PML died. All patients belonged to the 3000 patients' cohort reaching three or more years of continuous therapy with efalizumab. Furthermore, the manufacturer Genentech, Inc. has voluntarily withdrawn efalizumab from the US market as of April 2009.

5. Expert opinion

Efalizumab represents the prototype of T-cell targeted therapy in psoriasis. The efficacy and safety of efalizumab have been demonstrated both in clinical trials and in several years of off-trial experience. Efalizumab showed an efficacy in ~ 60% of treated patients, defined as responders. In these patients, efalizumab led to an almost complete clearance of skin lesions that was maintained long term in the vast majority of responders. The long-term efficacy and stability of response to efalizumab were peculiar features of this drug. Different from patients treated with anti-TNF drugs who often show relapses of the disease during the course of therapy, patients under long-term efalizumab never experience relapses. This correlates with a great improvement in quality of life indexes.

The second important point to consider is related to the safety: contrary to what is expected for a T-cell targeting immunosuppressive drug, the number of infectious adverse events observed during trials and in post-trial clinical use was surprisingly low. There were no signals for bacterial or common viral infections or opportunistic infections specifically associated with efalizumab treatment. In the same line proceeds the lack of significantly increased risk for neoplasms (excepting the slight increase in cutaneous neoplasms).

However, the adverse event leading to efalizumab withdrawal was the diagnosis of three cases of PML, a fatal neurologic disease caused by the reactivation of JC virus in the brain. This virus, which is present in a large proportion of population in inactive status, is reactivated following immunosuppression and leads to a progressive demyelinating disease resulting in death. The mechanisms of virus reactivation are largely unknown. Because cases of PML were observed in patients treated with drugs affecting T-cell trafficking (natalizumab and efalizumab), it is reasonable to hypothesize that specific subsets of T cells are required to control virus reactivation. Similarly, because this virus is reactivated only in a very small proportion of immunodepressed patients, other factors, for example, genetic background, besides immunosuppression, are likely to be required for virus reactivation. A strong research effort is, therefore, necessary to identify the exact mechanisms underlying JC virus reactivation and patients at high risk of reactivation.

This will allow designing T-cell targeting drugs which leave intact the capability of immune system to control JC virus reactivation and to avoid T-cell targeting therapies in high risk patients.

Based on our personal experience, efalizumab gave us two main lessons: i) long-term continuous treatment of psoriasis is the preferable mode of treatment in moderate-to-severe plaque psoriasis, ensuring the maximum benefit for patients

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and ii) off-trial long term monitoring of adverse events is the key to evaluate the safety of psoriasis drugs.

In conclusion, we think that efalizumab represented a proof of principle confirming the effectiveness of T-cell targeting strategy for the treatment of psoriasis indicating that more research is needed to bypass potential risks linked to this therapeutical strategy. It is, therefore, possible that new advanced T-cell targeting drugs will be added to the psoriasis armamentarium in the near future.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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