Foreword

Foreword

Professor Georg Stingl
pages iii–iii

Efalizumab in routine use: a clinical experience

N. Selenko-Gebauer, F. Karlhofer and G. Stingl
pages 1–6

Efalizumab in the treatment of chronic plaque psoriasis: experiences from the largest psoriasis treatment centre in Denmark

Knud Kragballe
pages 7–11

The Greek experience with efalizumab in psoriasis from a University Dermatologic Hospital

C. Antoniou, I. Stefanaki, A. Stratigos, G. Avgerinou, P. Stavropoulos, I. Potouridou, D. Polidorou, A.E. Moustou, M. Kosmadaki and A.D. Katsambas
pages 12–16

Long-term treatment of plaque psoriasis with efalizumab: an Italian experience

pages 17–23

Managing moderate-to-severe psoriasis with efalizumab: experience at a single Spanish institute

C. Ferrándiz and J.M. Carrascosa
pages 24–29
In 2004, efalizumab, a recombinant, humanized anti-CD11a monoclonal antibody, was approved by the EMEA for the treatment of patients with moderate-to-severe plaque psoriasis. This approval was based on the results of several well-designed and well-performed clinical studies. Such trials, however, do not necessarily reflect the everyday situation in the physicians’ private office.

In this supplement to the British Journal of Dermatology, university-based dermatology hospitals from five European countries report on their experience with efalizumab in routine clinical practice. The conclusions drawn by the various investigators are quite similar: (i) efalizumab is an efficacious therapy for patients with moderate-to-severe, stable plaque psoriasis and has an easily manageable safety profile; (ii) in patients who respond well to efalizumab during the first 12 weeks of treatment, the therapeutic success can usually be maintained by continued treatment for a prolonged period of time; (iii) efalizumab should not be used in patients with eruptive, unstable forms of the disease and in patients with joint disease.

Physicians prescribing this form of therapy should be aware of the fact that efalizumab recipients often exhibit flu-like symptoms after the first few injections and develop a reversible form of leukocytosis as consequence of the impaired tissue homing of pathogenic leukocytes. On the skin itself, one must distinguish between harmless and transitory papular eruptions, true disease flares and, rarely, rebounds that may occur after abrupt treatment interruption and preferentially in patients with unstable disease. The articles contained in this supplement also provide useful advice on how to deal with such situations.

Professor Georg Stingl
Medical University of Vienna, Austria
Efalizumab in routine use: a clinical experience
N. Selenko-Gebauer, F. Karthofer and G. Stingl

Division of Immunology, Allergy and Infectious Diseases, Department of Dermatology, Medical University of Vienna, Vienna, Austria

Summary

With the advent of biological therapies, continuous long-term control of psoriasis is now becoming a reality. We report our experience with biologics based on the treatment of more than 550 psoriatic patients with such compounds at our special outpatient care center of Bio-Immunotherapy at the Department of Dermatology of the Medical University of Vienna. Approximately 220 of these patients are currently receiving efalizumab. In our hands, efalizumab was generally found to be safe and well tolerated and, after 12 weeks of treatment, resulted in a PASI reduction of 50% or more in approximately two-thirds of patients treated. In most of these ‘early’ responders, the therapeutic efficacy of efalizumab can be maintained for a prolonged period of time, in certain patients up to 36 months. Flares occurring during long-term therapy were rare and, in most instances, triggered by infections. During such flares, we usually do not discontinue efalizumab therapy, but rather try to combat the infection by appropriate antibiotics and to control the activity of the cutaneous eruption by the addition of topical (corticosteroids) and, when needed, systemic (e.g. methotrexate 15–20 mg week⁻¹ for 8–10 weeks) medication. In such a situation, it is of utmost importance for the care-taking physician to closely communicate with the affected patients in a scientifically competent fashion and to have an open ear for their concerns. This helps and improves patient compliance and minimizes the need for treatment discontinuation.

Psoriasis is a chronic, incurable, inflammatory skin disorder that often requires long-term therapy for effective symptom control. Psoriasis affects about 1–3% of the general population.¹ ² The impact of psoriasis on a patient’s quality of life is thought to be comparable with that of diseases like bronchitis, diabetes and asthma.³

Traditional treatments for moderate-to-severe psoriasis involve phototherapy (PUVA) and systemic therapies such as methotrexate and cyclosporin. These conventional therapies mostly provide effective relief of disease symptoms, but can be associated with significant treatment-related organ toxicity,⁴ thus making them unsuitable candidates for long-term therapy. Rotational, combination, sequential or intermittent treatment strategies have been used to limit toxicity, but these approaches lead to cycles of relapse and remission, and, consequently, have a major impact on the patient’s quality of life. These limitations created a need for a psoriasis treatment that is safe and effective for long-term administration.

Advances in cellular and molecular research have resulted in the development of biologics, a new class of protein therapeutics, designed specifically for interference with the key players of the inflammatory disease process. The first biologic agent to be approved in Europe for the treatment of moderate-to-severe psoriasis was efalizumab (Raptiva®, Industria Farmaceutica Serono S.p.A., Rome, Italy). In Austria, it was introduced in 2004. Efalizumab is a recombinant, humanized monoclonal antibody that targets the alpha-subunit (CD11a) of the leukocyte function-associated antigen-1 (LFA-1). By blocking the interaction of CD11a and intercellular adhesion molecule-1 (ICAM-1), efalizumab interferes at multiple levels with the pathogenesis of psoriasis, inhibiting leukocyte trafficking into the skin as well as the continuous activation of T-lymphocytes by antigen-presenting cells in the dermis and epidermis.⁵ Efficacy and safety of efalizumab have been demonstrated in numerous clinical trials, the longest of which demonstrated maintenance of effect for 36 months.⁶⁻¹¹ Safety data indicate that efalizumab is generally well-tolerated, is associated with a low incidence of clinically significant adverse events and shows no evidence of cumulative or end-organ toxicity over a period of 36 months of continuous treatment.¹²

This clinical success has changed the paradigm from the traditional therapy of inflammatory episodes to continuous long-term control of psoriasis, which is now becoming a reality.

When biologics became available for the treatment of psoriasis patients, we established at our department a clinic for Bio-Immunotherapy specializing on this group of patients.
We are currently treating more than 550 psoriasis patients with biologic therapies in this unit, approximately 220 of whom are receiving efalizumab.

**Patient selection**

Efalizumab is indicated for use in adults with moderate-to-severe plaque psoriasis who are eligible for systemic therapy and considered as 'high need'.13,14 This indicates that in these patients one or more traditional systemic treatments (e.g. methotrexate, cyclosporin, PUVA) either provided no major benefit, was accompanied by severe side effects or could not be administered because of existing contraindications. These include kidney and liver damage as well as the existence of a 'metabolic syndrome', a combination of arterial hypertension, diabetes, hyperlipidaemia, hypercholesterolaemia, and obesity.

Due to its dosing per body weight, efalizumab can be adequately tailored to the actual need of a given patient. This is why we often use efalizumab as a first line biologic in obese patients. We tend to initiate efalizumab mainly in patients with stable disease and never in patients with pustular psoriasis or psoriatic arthritis. Rarely, we decided to administer efalizumab in patients with a more active disease process and have seen good results by combining it with methotrexate in a dosage of 15–20 mg week\(^{-1}\), depending on the extent of disease and body weight of the patient (Fig. 1). We sometimes use this approach in patients who have comorbidities (e.g. latent tuberculosis (without active disease, defined as positive PPD and normal chest X-ray), demyelinating disease, heart failure, or chronic hepatitis B or C) that may rule out treatment with other biological therapies, such as tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) blocking agents. We have no experience with cyclosporin or PUVA as comedication during the efalizumab initiation phase.

We also used efalizumab in patients with recalcitrant palmoplantar disease and have seen mixed responses. Although detailed data are lacking, it is our impression that the therapeutic effect is comparable with that seen with TNF-\(\alpha\) blockers, but recurrences under continued treatment do occur earlier with the latter.

**Treatment initiation, patient information**

Before initiating treatment with biologics, the dermatologist needs to assess the patients’ disease state and educate them about rationale, type and application of the respective form of therapy. The majority of patients selected for efalizumab treatment are ‘high need’, but without systemic treatment at time of efalizumab initiation. One reason for this is that many patients have resigned to the presumed fact that there is no effective continuous treatment for their disease. We should also keep in mind that physicians in private practice have become reluctant to prescribe systemic anti-psoriatic medication in their offices.

When we decide to put a patient on efalizumab, it is particularly important to ensure that he/she understands that psoriasis is a life-long condition for which there exists currently no cure, which implies that long-term treatment may be needed. A close dialogue on biologic therapy between the dermatologist and the patient is mandatory, since efalizumab is a drug exclusively used by dermatologists, and other medical specialists are often not adequately informed about its mechanism of action and/or risk profile. During initiation of efalizumab, the patient should be made aware of the fact that flu-like symptoms can occur during the first 3–4 weeks of treatment and that there exists, at least theoretically, the risk of a higher incidence of infections.

Efalizumab is initiated as monotherapy in patients with stable plaque psoriasis. In patients with a more active disease process we have seen good results by initiating efalizumab in combination with methotrexate, slowly tapered off after 6–8 weeks.

---

*15–20 mg week\(^{-1}\) for 8 weeks, then taper.
**Treatment administered by a healthcare worker at the inpatient department.
MTX, methotrexate; PASI, psoriasis area and severity index; PUVA, psoralen ultraviolet A therapy; TNF, tumour necrosis factor.

Fig 1. Practical scheme of efalizumab patient management.
In case of an ongoing systemic anti-psoriatic therapy and the need for a shift to efalizumab, it is important to prevent re-emergence of symptoms during this transition period. To this end, we do usually overlap two forms of treatments allowing efalizumab enough time to reach efficacy and prevent rebound from discontinuation of the previous therapy.

In the case of PUVA, where disease clearance normally exceeds the treatment period, a rather abrupt switch to efalizumab is possible. In the case of cyclosporin or methotrexate, however, an overlap and slow dose reduction of the prior agent has been shown to be beneficial.\(^\text{15}\)

The licensed dose of efalizumab is 1 mg kg\(^{-1}\) administered once-weekly as a subcutaneous injection.\(^\text{13,14}\) Treatment starts with a single conditioning dose of 0.7 mg kg\(^{-1}\), which has been reported to reduce the risk of acute injection-related side-effects.

**Response evaluation**

A patient’s response to efalizumab is assessed using the Psoriasis Area and Severity Index (PASI) and Physician’s Global Assessment (PGA). After the first 12 weeks of treatment, we consider patients responding to treatment to be those who show a PASI reduction of at least 50% (PASI-50) or a PGA rating of ‘good’ or better. This happens, in our experience, in approximately two-thirds of the patients treated. In such patients efalizumab therapy is being continued. Based on our and other investigations, abrupt discontinuation of efalizumab frequently results in disease flares and arthralgia. We therefore instruct the patients that efalizumab treatment must not be interrupted, unless the care-taking physician would decide differently.

Blood counts are checked regularly, with special attention to lympho-/leukocyte counts, thrombocytes, liver function parameters and creatinine levels. A regular protein electrophoresis to exclude paraproteinaemia is performed.

During the first 12 weeks we check blood parameters monthly, thereafter the scheme is widened up to every 3 months. In approximately half of patients, treatment with efalizumab leads to a dose-dependent increase in the total white blood cell count. This has no correlation with the responder status and can be up to 3.5-fold higher than the upper limit of normal. Leukocytosis is transient, reversible and clinically asymptomatic.\(^\text{14}\) The effect is thought to be caused by an efalizumab-induced interference with the interaction of leukocyte-bound CD11a and ICAM-1 expressed by endothelial cells, resulting in the inhibition of attachment and diapedesis of white blood cells.

After treatment discontinuation, leukocyte levels generally return to baseline. So far, no long-term sequelae of this haematological event have been reported.\(^\text{14,16}\)

**Treatment responders**

In the phase III clinical trials of efalizumab conducted so far, the majority of patients with moderate-to-severe psoriasis experienced a marked clinical benefit with efalizumab; up to 82% of patients who received efalizumab achieved a PASI-50 response within 12 weeks.\(^\text{6,9,10}\) Data from a 36-month, open-label, phase III trial demonstrate that this benefit is usually maintained in the long-term with continuous efalizumab therapy.\(^\text{8}\) A direct comparison of these data with those obtained with conventional systemic therapies is difficult, because there exist mainly short-term safety and efficacy data for the latter.\(^\text{17,18}\)

In our hands, approximately two-thirds of the patients initiated with efalizumab stay on treatment after 12 weeks, presenting a PASI reduction of 50% or more. In stable psoriasis, upon initiation of efalizumab, we have not seen any significant differences in clinical response probability concerning the extent of disease. However, it seems that patients with large involvement of BSA, yet rather limited thickness of plaques, are particularly prone to respond to efalizumab even within the first 6–8 weeks. Once a patient responds to efalizumab and treatment administration is performed regularly and continuously, efficacy is usually maintained for a prolonged period of time.

In early efalizumab responders, we have rarely, if ever, encountered a slow and insidious reappearance of lesions that could be interpreted as loss of efficacy. Occasionally, however, we experienced disease flares and localized papular eruptions (see below).

**Non-responders – inflammatory non-responders**

Patients who show no noticeable response after 12 weeks of treatment (PASI reduction <50%) are unlikely to derive benefit from continued efalizumab and the care-taking dermatologist should consider switching them to an alternative therapy. In our clinical practice, we have identified a small (2–5%) subgroup of non-responders, the so-called ‘inflammatory non-responders’, which not only do not respond to efalizumab, but even develop a more inflammatory skin status with each single injection of efalizumab (Fig. 1). In this event, our experience has taught us to discontinue efalizumab treatment already at week 8 and taper to another systemic treatment, e.g. cyclosporin (5 mg kg\(^{-1}\)) or infliximab (5 mg kg\(^{-1}\) +/− MTX), mostly keeping the patients on our ward for a few days.

**Adverse events – infections**

Every compound that interferes in one way or the other with phenotype and function of immunocytes raises concerns about its promoting the outbreak of infectious disease processes. In a review of four placebo-controlled, 12-week trials, the incidence of infection was similar in patients who received efalizumab (28.9%; 0.4% serious) and those who received placebo (26.3%; 0.1% serious). The rate of infections did not increase with extended treatment (up to 27 months of continuous treatment). Notably, there were no reported cases of tuberculosis, Pneumocystis carinii, histoplasmosis or toxoplasmosis...
in these clinical trials with efalizumab. In the recently published CLEAR trial the incidence of infection-related adverse events within the first 12 weeks of treatment is slightly elevated in efalizumab-treated patients compared to the placebo group. These data are in keeping with the observations made in our cohort. Among 220 efalizumab recipients, we have experienced one case of sterile meningitis and decided to stop efalizumab treatment. Apart from this, we have not experienced any severe or opportunistic infection or reactivation of latent tuberculosis. We tend to continue efalizumab treatment during mild to moderate infections prescribing antibiotic therapy in parallel. As opposed to the use of TNF-α blockers, no treatment interruption is necessary in the case of elective surgery and to date, at our centre, no wound infections have occurred during this process.

Malignancy

Moderate-to-severe plaque psoriasis is associated with an increased risk of cutaneous or systemic malignancy, and immunosuppressants used to treat psoriasis (e.g. cyclosporin, methotrexate, PUVA) can potentially increase this risk. In a pooled analysis of multiple phase III open-label and placebo-controlled clinical trials it was found that efalizumab treated patients had an increased risk of cutaneous or systemic malignancy, as compared to the placebo. In the recently published European ‘Clinical Experience Acquired with Raptiva’ (CLEAR) study, arthralgia was reported in 7.4% of patients treated with efalizumab (compared to 3.0% of those receiving placebo).

What is the nature of this event? It might be the precipitation of psoriatic arthritis by efalizumab or a distinct entity as a side effect of the treatment. Although accurate data are lacking, we tend to favour the latter: Affected patients describe joint stiffness and pain, but dactylitis or enthesitis, classical clinical signs of psoriatic arthritis are only rarely observed. In most cases large joints such as knees, elbows and shoulders are involved, whereas distal interphalangeal joint involvement is the exception. Skeletal X-ray examinations of the affected joints are usually without pathological findings.

We initially try to reverse the joint pain with non-steroidal anti-inflammatory drugs (NSAIDs). Diagnostic procedures are conducted in parallel, such as skeletal X-ray of hands and feet to exclude joint erosions, as well as a repeated blood serology for rheumatic diseases (rheumatoid-factor, anti-CCP, ANA, sedimentation rate).

As opposed to the situation in rheumatoid arthritis and psoriatic arthritis patients, this therapeutic approach is usually successful. In recalcitrant cases, however, efalizumab discontinuation or shift to anti-TNFs or methotrexate should be considered.

Thrombocytopenia

Rare cases of thrombocytopenia associated with efalizumab treatment have been reported and, in clinical trials, thrombocytopenia with platelet counts of less than 52 000 per μL was observed in 0.3% of patients. To date, at our centre, we have experienced only one single case of thrombocytopenia caused by efalizumab. Frequent monitoring of platelet counts is recommended, with more frequent monitoring during the first 3 months of treatment (monthly for the first 12 weeks, then every 3 months thereafter). If thrombocytopenia does occur, efalizumab treatment must be stopped.

Skin side effects – localized papular eruptions, generalized inflammatory flare

Also at our centre we have observed two different types of cutaneous adverse events in psoriasis patients responding to efalizumab: (I) Transient, localized, papular eruptions and (II) Generalized inflammatory exacerbations (Fig. 1). These events are rare and differ in localization, appearance, severity and management.

I) Transient localized papular eruptions have occurred in approx. 5% of efalizumab-treated patients and can present at
any time throughout treatment (Fig. 3). These eruptions tend to be localized on the intertriginous areas, and usually occur outside of areas of existing plaques. Histologically, they represent inflammatory psoriatic plaques and can be effectively managed by adding concomitant topical therapy until symptoms resolve. There is no need for efalizumab discontinuation.

(II) Generalized inflammatory flares have occurred in up to 3% of efalizumab-treated patients. This event typically presents as widespread, erythematous, edematous lesions, and involves existing plaques (Fig. 2). We have observed such exacerbations in long-term treatment responders, where they mostly were triggered by infections. A generalized inflammatory flare can be managed successfully with a short course of conventional systemic treatment (e.g. methotrexate) in many cases, which is administered without discontinuing efalizumab and tapered off, once symptoms are under control. However, if symptoms do not improve, efalizumab should be stopped and alternative systemic therapies considered.

Rebound, treatment discontinuation

86% of the efalizumab recipients who achieved a PASI-75 response by week 12 in clinical trials relapse after termination of efalizumab treatment after a median time of 67 days. A so-called ‘relapse’ includes any type of reoccurrence of the disease, mostly plaques and papules appearing steadily and continuously. By contrast, ‘rebound’ is an abrupt worsening of the disease after treatment discontinuation defined by a PASI 125% to baseline. It occurs in about 14% of patients on discontinuation of efalizumab therapy and, on average, within the first weeks after treatment is stopped. Rebound may occur in any patient that is discontinued from efalizumab, responders as well as non-responders. The dermatologist must be aware of this possibility and needs to observe the patient carefully. To avoid rebound, it is important to devise strategies which minimize the need for discontinuation of efalizumab treatment (e.g. approaches for managing adverse events). However, for some patients, temporary or permanent treatment discontinuation may be necessary. For example, pregnancy, extended travel plans or vaccination may warrant temporary interruption of therapy. If discontinuation of efalizumab is unavoidable, close observation is advised and initiation of alternative treatment should be considered, if symptoms worsen. A number of commonly used anti-psoriatic treatments can be used to prevent rebound. In patients who initially responded well to treatment but for whom treatment discontinuation is subsequently necessary, efalizumab can be restarted again at a later date, with symptom relief comparable to that achieved with the initial course of treatment.

Conclusion

In our hands efalizumab was generally found to be safe and well tolerated, with two-thirds of patients achieving a PASI-50 response after 12 weeks of efalizumab treatment. Efalizumab is a safe and effective drug in patients with stable moderate-to-severe plaque psoriasis. We see a clear treatment niche for efalizumab in obese patients, in patients in whom anti-TNF-α agents are contraindicated, and, perhaps, in certain individuals with recalcitrant palmoplantar disease. Currently, we are managing long-term responding patients that have been receiving continuous efalizumab treatment for more than 36 months. An adequate clinical experience is necessary to manage adverse events, help patient compliance and minimize the need for treatment discontinuation. Overall, our experiences with efali-
Efalizumab provide evidence of the success of this agent as a continuous treatment option for the long-term control of psoriasis.

References
14 Raptiva EMEA approved product information, http://www.emea.com
Efalizumab in the treatment of chronic plaque psoriasis: experiences from the largest psoriasis treatment centre in Denmark

Knud Kragballe
Department of Dermatology, Marselisborg Center, Aarhus University Hospital, Aarhus C, Denmark

Correspondence
Knud Kragballe
E-mail: ovl12kkr@ac.aau.dk

Accepted for publication
11 January 2007

Key words
chronic plaque psoriasis, Denmark, efalizumab

Conflicts of interest
KK has participated in clinical trials and served as a consultant and speaker for Merck Serono*, Centocor, Schering-Plough, Abbott, Leo Pharma and Novo Nordisk.
*Merck Serono International SA, an affiliate of Merck KGaA, Darmstadt, Germany.

Summary

About 20–30% of patients with chronic plaque psoriasis have severe forms of the disease and require systemic treatment. The long-term use of conventional systemic therapies is limited by toxicity, and many patients are resistant to these treatments. New biological agents, such as efalizumab and infliximab, offer a more targeted approach than conventional therapies and are more suitable for long-term, continuous treatment. At our hospital, we started treating patients with efalizumab in 2003 as part of a clinical trial programme and report here our experiences with this agent in 31 patients we have treated over the last 3 years. Here we share our standard procedures for patient selection, screening and treatment initiation, and report the efficacy and safety of efalizumab in our patients. Several case studies are presented to illustrate specific points of interest, such as the use of efalizumab in unstable psoriasis and management of arthropathy events. Finally, we suggest a number of approaches that may help to maximize the chances of long-term success in patients receiving efalizumab. In our hands, efalizumab has proven to be an effective therapy in the majority of patients (>70%). The majority of these patients move to continuous efalizumab therapy (77%), the longest duration of which is currently 18 months. The main advantage of efalizumab over tumour necrosis factor-blockers is the lower risk of serious side-effects. By devising and disseminating effective strategies for the management of patients receiving efalizumab therapy, we hope this treatment will offer patients a truly continuous, long-term solution to their disease.

Chronic plaque psoriasis is a lifelong disorder that requires continuous management. Approximately 20–30% of patients with chronic plaque psoriasis have moderate-to-severe forms of psoriasis,1 which has a greater impact on a patient’s quality of life than less severe forms of the disease.2 These more severe forms of psoriasis require treatment with systemic therapies for symptom control, as topical treatment is often suboptimal.3 Conventional systemic therapies, such as methotrexate and cyclosporin, are effective, but their long-term use is limited by their toxicity and many patients are resistant to these treatments.1,4 New biological agents offer a more targeted approach to treatment than conventional therapies. Because they act at specific points in the disease pathway, this new class of agent has improved safety profiles and is more suitable for long-term, continuous therapy.4,5

Approximately 1–3% of Europeans have psoriasis,6 with prevalence being particularly high in certain Northern European countries. A study in the Faroe Islands reported a prevalence of 2.8%.7 An even higher prevalence was reported in a Danish study, which found psoriasis in 2.5% of Danish women and in 3.2% of Danish men.8 This variation between countries may be a result of differences in diet, climate and genetics, or, mostly likely, a combination of all of these factors.

In September 2004, the biological agent efalizumab was approved for the treatment of psoriasis in Europe, and is now available in more than 50 countries worldwide, including Denmark. In Denmark, efalizumab was prescribed initially only by hospital-based dermatologists, although dermatologists in private practice can now offer this treatment to their patients. At our hospital, we first started treating patients with efalizumab in 2003 as part of a clinical trial programme and report here our experiences with this agent over more than 3 years.

Which patients do we treat?

In our hospital, we use efalizumab and other biological agents for the treatment of adults with more severe forms of psoriasis, considering various factors such as symptom severity, disease activity, and previous treatment responses.
of chronic plaque psoriasis who have failed to respond to, who have a contraindication to, or who are intolerant to other systemic therapies, including cyclosporin, methotrexate and psoralen ultraviolet A (PUVA). These patients are divided into two groups prior to treatment assignment: those who have unstable psoriasis or a history of psoriatic arthritis are screened for tumour necrosis factor (TNF)-blocker eligibility and those who do not are screened for efalizumab eligibility.

To assess eligibility for efalizumab, patients are screened for hepatitis and HIV infections, and a chest X-ray is conducted. Note that this procedure is similar to that for TNF-blocker screening, although a tuberculin skin test is not required prior to efalizumab treatment. When assessing for efalizumab eligibility, we only conduct a tuberculin skin test in those patients we consider to be at risk of tuberculosis.

Of the 31 patients we have treated with efalizumab, 30 had plaque psoriasis and one patient had generalized pustular psoriasis. Among the 30 patients with plaque psoriasis, two patients also had pustular palmoplantar psoriasis, and one patient had erythrodermic psoriasis.

**How is treatment started?**

In patients who are already receiving methotrexate and who have partially responded to this treatment, efalizumab therapy is started and methotrexate stopped when a response is evident. The period of overlap between treatments is usually 8–12 weeks. In patients who have failed to respond to methotrexate, treatment is stopped abruptly and efalizumab started immediately. A similar approach is used for transitioning off other systemic therapies, such as cyclosporin.

**How effective is treatment?**

In February 2005, the first patient received efalizumab at our hospital outside the clinical trial setting. Since then, we have treated a total of 31 patients, 22 of whom responded to treatment by week 12 (71%). To date, 17 responding patients are described below. Based on these experiences, we feel strongly that both the patient and the physician should be involved in the decision of whether or not to continue efalizumab therapy.

**Case studies**

**Satisfied 'non-responders’**

A woman aged 39 years had moderate-to-severe plaque psoriasis, with a disease duration of more than 10 years, and which included psoriasis involvement on her exposed skin (hands, arms, lower legs and feet). Previously she had received phototherapy (UVB and PUVA) without effect and methotrexate treatment had been discontinued because of liver toxicity. Cyclosporin was not tried because of hypercholesterolaemia. Efalizumab (0.7 mg kg\(^{-1}\) per week for the first week, then 1 mg kg\(^{-1}\) per week) was initiated and after 12 weeks her Psoriasis Area and Severity Index (PASI) score had reduced from 15 to 8 (47% reduction; Fig. 1a, b). Although she did not achieve a 50% reduction in PASI score (PASI-50) and, therefore, might be considered a non-responder according to this measure, she was satisfied with her treatment as the plaques on her exposed areas were almost clear. The patient has continued to receive treatment successfully. At her last visit, 1 year after efalizumab was started, there were slightly indurated lesions on her trunk but the exposed skin areas remained clear; the patient was extremely satisfied with her appearance.

A man aged 51 years had severe plaque psoriasis for more than 20 years. Because of a high alcohol intake, his compliance with treatment was poor and methotrexate was contraindicated. Therefore, his psoriasis necessitated an average of three hospital visits per year. Efalizumab (0.7 mg kg\(^{-1}\) per week for the first week, then 1 mg kg\(^{-1}\) per week) was initiated and after 12 weeks the patient achieved a 40% reduction in PASI score (from 25 to 15). Despite this, the patient was satisfied with the treatment and the decision was taken to continue therapy. More than 1 year later, the patient is still receiving efalizumab therapy and his symptoms are effectively controlled (PASI = 12 at last visit; 52% reduction). Since starting efalizumab treatment, the patient has not required hospitalization.

**Can patients with unstable disease benefit from efalizumab?**

It is a widely held perception that patients with unstable psoriasis may not benefit from several of the biological agents (efalizumab, etanercept, alefacept) because these agents are not as fast-acting as other systemic therapies available (cyclosporin, infliximab). Therefore, many dermatologists tend to avoid prescribing efalizumab to patients with unstable disease. However, we have used efalizumab in a patient with tend to avoid prescribing efalizumab to patients with unstable disease. However, we have used efalizumab in a patient with
unstable psoriasis and found it to be of value. This case is described below.

Efalizumab in unstable psoriasis

A man aged 41 years had unstable, almost erythrodermic, plaque psoriasis. The patient had previously failed treatment with UVB, PUVA and methotrexate because of lack of efficacy. Cyclosporin treatment was contraindicated because of hypertension. The patient’s skin was very itchy and he had been on sick leave for several months. Efalizumab (0.7 mg kg\(^{-1}\) per week for the first week, then 1 mg kg\(^{-1}\) per week) was initiated, and 12 weeks later his psoriasis was almost clear, except for lesions on the lower legs. The patient has continued to receive efalizumab therapy and had a PASI score of 2 at the last visit, 48 weeks after starting therapy. The patient has now returned to his full-time job as a store man.

Finding alternatives to stopping efalizumab

Given the history of systemic psoriasis treatment, physicians are used to switching patients between therapies when treatment fails. The new biological treatment paradigm provides us with safer therapies and encourages us to persevere with treatment, favouring trouble-shooting over discontinuation. In most cases, patients are happy with these new biological treatments, they are tired of stopping and switching, and want to stay on a treatment that works. How, then, can we maximize the chances of long-term success in patients receiving efalizumab?

Firstly, we can try continuing therapy in patients who initially show a partial response, as some of these patients may respond further after the initial 12-week period. For example, in the CLEAR study, of the patients who failed to achieve PASI-50 after 12 weeks of efalizumab treatment, 12.8% achieved PASI-75 and 43.6% achieved PASI-50 with continued treatment.\(^9\)

Fig 1. A woman with exposed skin involvement in her psoriasis, who did not achieve a 50% reduction in Psoriasis Area and Severity Index (PASI) after 12 weeks of efalizumab treatment, but was satisfied with treatment because her exposed lesions were almost clear from psoriasis. (a) Before treatment (PASI = 15); (b) after 12 weeks of efalizumab treatment (PASI = 8).
Secondly, we can ensure that patients have realistic expectations about their treatment, they are aware of the potential side-effects they may experience with efalizumab, and are supported and encouraged to report any events during the course of their treatment. If this is not done, patients may be alarmed at the occurrence of events, such as transient papular eruptions or injection-site reactions (although rare), and stop treatment unnecessarily. In our hospital, patients eligible for efalizumab therapy attend an initial session with a nurse, who explains all aspects of the treatment and teaches the patient how to administer their injections. Visits with the nurse are then scheduled 4 and 8 weeks into the treatment course, and a visit with both the physician and the nurse is scheduled for week 12. After this, visits with the physician take place every 3 months. To support patients and encourage the reporting of adverse events, we provide a hotline that patients can call at any time during their treatment.

Finally, and most importantly, we can share our experiences and knowledge to help develop strategies for managing adverse events without treatment discontinuation.

Worsening of psoriasis while on therapy has been reported in about 3–5% of patients during Phase III clinical trials. We observed psoriasis worsening in 5/31 patients (16%). In cases where sporadic recurrence of psoriatic plaques occurs, we treat patients with a short course of methotrexate, which is stopped once symptoms resolve. This strategy has also been used successfully by other groups. In patients who experience a localized recurrence, we have successfully used topical corticosteroids or calcipotriol/betamethasone to treat psoriasis worsening. However, persuading patients to revert back to the use of creams or ointments when they feel they have moved on from this inconvenient and uncomfortable approach can be difficult. For patients who experience severe, generalized inflammatory flare, cyclosporin is added. When the disease is then under control, efalizumab is stopped and a TNF-blocker is initiated (provided the patient is eligible for this treatment). Cyclosporin is usually tapered off 4–8 weeks after the TNF-blocker is started.

Of the 31 patients we have treated, 3/31 (10%) have experienced a transient, localized, papular eruption while on therapy. This is lower than the figure reported by Hamilton,10–12 and knowledge to help develop strategies for managing adverse events without treatment discontinuation.

Managing adverse events

Although we generally avoid the use of efalizumab in patients with psoriatic arthropathy, we took the decision to

Conclusions

A total of 31 patients with chronic plaque psoriasis have been treated with efalizumab at our hospital over the last 3 years outside the clinical trial setting. To date, the longest duration of continuous efalizumab therapy is 18 months. In our hands, efalizumab has proven to be an effective therapy in the majority of patients (71%). The main advantage of efalizumab over TNF-blockers is the lower risk of serious side-effects with efalizumab. Patients with chronic plaque psoriasis requiring systemic treatment want continuous long-term control of their symptoms, without the need to switch or revert to previous therapies. Biological therapies offer to deliver this promise and, indeed, in our hands the majority of patients who responded to efalizumab (77%) have gone on to receive continuous, long-term efalizumab treatment.

By devising and disseminating effective strategies for the management of patients on efalizumab therapy, we believe this treatment will offer patients a truly continuous and long-term solution to their disease.

References

The Greek experience with efalizumab in psoriasis from a University Dermatologic Hospital

C. Antoniou, I. Stefanaki, A. Stratigos, G. Averginou, P. Stavropoulos, I. Potouridou, D. Polidorou, A.E. Moustou, M. Kosmadaki and A.D. Katsambas

Department of Dermatology, Andreas Sygros Hospital, University of Athens, Greece

Correspondence
Christina Antoniou
E-mail: phbiolun@otenet.gr

Accepted for publication
11 January 2007

Key words
efalizumab, psoriasis, therapy

Conflicts of interest
The authors have no conflicts of interest.

Summary

Background Efalizumab (anti-CD11a antibody) targets T cell-mediated steps important in the immunopathogenesis of psoriasis. As efalizumab is intended to be administered on a continuous long-term basis in psoriasis, it is important to share experience concerning issues commonly occurring during its use in real daily practice.

Objective To evaluate the efficacy and safety of efalizumab treatment in Greek patients with moderate-to-severe plaque psoriasis, and to investigate whether there are specific characteristics that predict the clinical outcome of therapy.

Patients Seventy-two patients with moderate-to-severe plaque psoriasis, who had failed to respond to, or had a contraindication to, or were intolerant to other systemic therapies, received efalizumab (1 mg kg\(^{-1}\) per week) for 12 weeks or more.

Results After 12 weeks of efalizumab treatment, 65% of patients achieved 50% or more improvement from baseline Psoriasis Area and Severity Index (PASI) and 39% achieved at least 75% reduction in PASI score. The mean percentage PASI improvement from baseline was 62%. The most common side effects were a flu-like syndrome, a transient localized papular eruption, leucocytosis and lymphocytosis. There was no correlation between the occurrence of these side effects and the clinical response. Patients with a past history of unstable types of psoriasis were likely poor responders to efalizumab, and at an increased risk of developing generalized inflammatory flare.

Conclusion These results confirm previous reports suggesting that treatment with efalizumab is an efficacious and safe option for patients with moderate-to-severe plaque psoriasis. A detailed previous history of psoriasis is important in order to select possible candidates for efalizumab therapy.

Psoriasis is a chronic autoimmune disorder with cutaneous manifestations. It affects 1–3% of the US and European population, and about 25% of patients have moderate-to-severe disease. These patients usually consider the disease uncomfortable and disfiguring, causing substantial problems in their everyday life, and resulting in lower quality of life. Despite the availability of therapeutic options, the long-term management of psoriasis is complicated by treatment-related limitations, while fewer than half of those affected by psoriasis find their treatment highly satisfactory. Taking also into account the chronic, with no cure nature of the disease and its frequent early onset, there is a substantial need for therapies that can be safely administered on a continuous long-term basis. Psoriasis has, therefore, recently become a focus for biological therapies using monoclonal antibodies that alter immune function.

The two major pathological lesions in psoriasis are epidermal hyperproliferation with abnormal differentiation, and inflammatory infiltration in the dermal and epidermal layers. These processes are modulated by activated T cells or antigen presenting cells, which release a variety of chemokines and cytokines that signal the hyperproliferation of keratinocytes, and ultimately lead to abnormal differentiation. Efalizumab is a humanized monoclonal IgG1 antibody that binds with high affinity to CD11a, the \(z\)-subunit of leucocyte function-associated antigen 1 (LFA-1). It targets psoriasis pathogenesis at multiple levels, inhibiting T-cell activation in lymph nodes, preventing binding of T cells to endothelial cells, blocking their trafficking from the circulation into psoriatic skin, and preventing their reactivation in the dermis and epidermis.
The efficacy and safety of efalizumab in psoriasis have been demonstrated in 15 clinical trials enrolling more than 3800 patients, while some of these patients have participated in the longest running clinical trial with any biologic agent in psoriasis, a 36-month, open-label Phase III trial. During the course of treatment, possible intercurrent events, like localized mild breakthrough or generalized inflammatory flare, can occur. Exacerbation of psoriasis (flare) during efalizumab therapy, and rapid recurrence of disease beyond baseline (rebound) after discontinuation, may be observed.

As the clinical feedback concerning the use of efalizumab in psoriasis is rapidly accumulating, it is important to create a foundation for dermatologists to make informed decisions on how to initiate efalizumab, control the events that may occur during therapy, and maintain its continuous use. Clinical trials are conducted in a controlled manner, involve patient populations selected with specific inclusion and exclusion criteria, and may not always accurately reflect the real daily practice. Our Hospital is a reference University Center for dermatological problems in the city of Athens, which has a population of approximately 2 700 000, while many difficult to treat cases are referred from other regions of Greece. The purpose of our review was to present our up to date experience with efalizumab treatment in patients with moderate-to-severe plaque psoriasis.

Selection of patients

From 9/2004 until 4/2006 72 patients were started on efalizumab at our Hospital. All patients were adults with at least 2 years duration of moderate-to-severe plaque psoriasis and in addition had failed to respond to, or had a contraindication to, or were intolerant to other systemic therapies. We excluded patients with guttate, erythrodermic, or pustular psoriasis as sole or predominant form of psoriasis, subjects who had a history of internal malignancy or melanoma, those with a history of opportunistic or clinically significant recurrent infections as well as pregnant and breastfeeding women.

Sufficient time was spent in discussion with each patient about the success rates of efalizumab, onset of action, duration of therapy and possible adverse events. A plan of treatment with efalizumab, as well as alternatives, was discussed and explained. Patients consenting to therapy were taught how to self-administer the drug and were notified to report to their physician immediately any significant clinical change in safety. In general, the convenient once-a-week dose, the limited number of required medical appointments and the lack of hepatic and renal toxicity were considered beneficial by patients.

Efalizumab therapy started at 0.7 mg kg\(^{-1}\) per week for the first dose, and thereafter 1 mg kg\(^{-1}\) per week for subsequent doses. Patients were monitored clinically; Psoriasis Area and Severity Index (PASI) scores, Physician’s Global Assessment of change (PGA), static Physician Global Assessment (sPGA) and Dermatology Life Quality Index (DLQI) were assessed, and routine laboratory tests were regularly performed.

Clinical outcome

Seventy-two (72) patients (50 males, 22 females, with mean age 49 years) received efalizumab for at least 12 weeks, when their response status was formally assessed. At this point, 65% (47/72) of efalizumab-treated patients achieved at least a PASI-50 improvement and 39% (28/72) reached a PASI-75 response with an overall median reduction of 62% in PASI score. Patients achieving > 50 PASI improvement with a PGA rating of Good, Excellent or Cleared at 12 weeks, continued on efalizumab, while non-responders discontinued efalizumab and were switched, if willing, to an alternative systemic therapy. PASI-75, while an efficacy criterion for success in many regulatory bodies, is very stringent. PASI improvement > 50 is generally considered satisfactory by patients, and it is unlikely that patients achieving this degree of improvement will lose disease control or experience rebound. In the occasional events that they missed a dose, we did not encounter any problems. Forty-seven patients continued on efalizumab therapy after week 12; at week 20, 93.6% (44/47) of them achieved at least a PASI-50 improvement and 68% (32/47) reached a PASI-75 response with an overall reduction of 81% in PASI score. We have patients on continuous treatment for 2 years.

DLQI: Patients reported 53% reduction in skin related limitations and psoriasis symptoms at 12 weeks compared with the beginning of therapy, allowing them to return to activities of daily living, such as sporting activities, work, and social relationships and also reported improved sense of well-being.

Adverse events

i) Adverse events not related to psoriasis

During the initial period of treatment, the most common adverse events, reported by patients, were acute flu-like symptoms. These included headache, chills, fever, nausea, myalgia, occurred within 2 days after the injection and lasted from a few hours to 3–4 days. 17 patients (24%) reported these symptoms, which were mild, and typically subsided by the third injection. Reassuring the patients about the transient nature of the problem and prescribing antipyretics are sufficient in managing the condition. None of our patients discontinued therapy due to this mild flu-like syndrome, or considered it a reason for a medical visit. Headache as the sole adverse event was reported by 10 patients (14%) and was mild to moderate. Pruritus was mentioned by one patient, was of mild intensity and responded to emollients.

Incidence of infections, a major issue of concern when treating with immunomodulators, is reported to be similar among psoriatic patients on efalizumab – even when administered for a long period of time like 27 months – and those receiving placebo (28.9% vs 26.3%, respectively). Six patients (8.3%) presented infection during efalizumab therapy. The most common were upper respiratory tract infections (four patients, 5.6%) that did not require discontinuation of
therapy. Two patients presented with herpes zoster during the 2nd and 7th month of efalizumab treatment (Fig. 1). Efalizumab was stopped for 2 weeks and the patients received systemic antivirals, without any sequel. Another patient was diagnosed with pneumonia during the 12th month of efalizumab. She was treated with antibiotics and the efalizumab regimen was discontinued permanently. No case of malignancy, either of the skin or of internal organ, was observed.

The most common laboratory deviations that we encountered during efalizumab therapy were lymphocytosis (46 patients, 64%) and leucocytosis (28 patients, 39%), which are anticipated due to efalizumab mechanism of action. These abnormalities were observed mainly during the first 3 months of efalizumab treatment and returned to normal during the following months. There was no correlation between the occurrence of those abnormal values and either response of patients to efalizumab or the development of clinical adverse events. We have not encountered any case of thrombocytopenia or anaemia during treatment with efalizumab, although some patients had a slight reduction of platelets count, which remained, nevertheless, within normal limits.

ii) Adverse events related to psoriasis

Localized mild breakthrough (LMB) or transient localized papular eruption

Eleven patients (15%) developed a papular eruption during efalizumab therapy, which was transient and regressed with continuation of efalizumab and topical application of corticosteroids. The rash called localized mild breakthrough (LMB) or transient localized papular eruption, presents with papules usually within the first months of treatment, which are typically located on the flexural areas, torso and the neck, often in previously unaffected areas, although any site of the body can be involved (Fig. 2). None of them progressed to a generalized inflammatory flare, whereas these patients usually show significant improvement of their original psoriatic plaques. When the eruption subsided, the patients were treated with efalizumab alone and remained well controlled. Only a female patient, aged 31, showed a papular eruption during the 3rd month that persisted to topical use of corticosteroids, so a short course of cyclosporin was added to efalizumab. The eruption finally subsided and cyclosporin dose was tapered and finally stopped. The patient remained on efalizumab and presented another LMB during the 13th month of therapy.

Figure clinical and histological Failure to recognize the subset of patients who develop transient localized papular eruption may lead to unnecessary discontinuation of efalizumab. LMB has not been shown to be an indicator or predictor of future psoriasis adverse events, rebound or generalized inflammatory flare (GIF).7

Generalized inflammatory flare (GIF) It has been described that a small proportion of patients may exhibit a worsening of psoriasis that involves a substantial inflammatory component without clearing of the original plaques, with or without appearing of new lesions, which has been called Generalized Inflammatory Flare (GIF).7 Such flares are estimated to occur in 1–3% of patients, usually within 6–10 weeks into efalizumab therapy and are typically observed in nonresponders. It is, therefore, mandatory to assess the patients carefully during this period, especially those who have not shown a significant clinical response to efalizumab. GIF can be managed by the addition of a short course of concomitant systemic therapy, such as cyclosporin or methotrexate. If the flare is controlled and psoriasis improves, the systemic therapy can be tapered off and the patient remains on efalizumab alone. If the GIF is not controlled, efalizumab should be stopped and
the patient transitioned to another systemic treatment. Alternatively, efalizumab could be discontinued from the beginning of GIF and the patient treated with a systemic regimen.\textsuperscript{8}

We have encountered three cases of GIF up to now (Fig. 3). Two female patients aged 28 and 60, presented with diffuse papular inflammatory lesions during the 19th and 9th month of efalizumab treatment, respectively (Fig. 3a and 3b). Both were responders to efalizumab, which was continued with the addition of cyclosporin for 4 weeks in the first case. Another female patient, aged 59, developed large inflammatory, indurated plaques at her face in the 3rd month of therapy (Fig. 3c). A biopsy of facial lesion was consistent with a diagnosis of psoriasis. The patient was treated with a potent topical steroid and later on with cyclosporin with modest improvement of the rash. The eruption finally resolved with discontinuation of efalizumab.

Interestingly, two of these patients reported having developed sometime in the past unstable types of psoriasis (inflammatory or pustular lesions).

Relapse of psoriasis Three patients (4.2\%) developed during the 18th and 19th month of treatment discrete thick plaques with coarse scaling on sites not previously involved (clinical photo). All of them had responded well to efalizumab until the time of the eruption. They were treated with a short course of cyclosporin, without discontinuing efalizumab. The eruptions were considered as relapse of psoriasis when patient lost more than 50\% of the improvement achieved since baseline, they cleared following the 8 weeks of cyclosporin and have not recurred up to now.

Rebound and exacerbation of psoriasis Rebound of disease is defined as worsening of disease in responders as assessed by > 125\% baseline PASI, or new pustular, erythrodermic, or more inflammatory psoriasis occurring within 2 months of stopping therapy. Exacerbation of disease is defined as disease worsening in nonresponders either during or after treatment, which is more inflammatory in nature, and occurring either within pre-existing plaques, at previously uninvolved sites, or as new morphologies of disease, compared with baseline.

Two patients (2.8\%) experienced rebound, manifested as erythroderma, 1 month after discontinuation of efalizumab, while one patient (1\%4\%) experienced exacerbation during the 2nd month of efalizumab therapy and was switched to cyclosporin.

Arthropathy Three patients (4.2\%) developed arthropathy during efalizumab therapy. A female, aged 70, developed mild arthropathy at phalangeal joints at the 7th month of therapy. She was treated with nonsteroidal anti-inflammatory drugs (NSAIDS) without stopping efalizumab, and had subsequent regression of pain.

A male patient, 44 years old, presented with acute inflammatory arthropathy of the knees. Efalizumab was discontinued and the patient started therapy with infliximab with clinical improvement. Another male, 40 years old, developed inflammatory arthropathy of the lumbar area. Efalizumab was stopped and he received cyclosporin, with improvement of symptoms. These patients had no history of arthropathy/arthritis.

Conclusions Our results support that efalizumab has a favourable safety profile and is successful for the management of moderate-to-
severe plaque psoriasis in the majority of the patients (47/72, 65% achieved PASI-50 at week 12), with efficacy improving further after continued therapy. Education of patients about the different possibilities of response and adverse events during and after stopping efalizumab is essential to facilitate adherence to treatment. Studies conducted in large series of patients with long treatment and observational periods confirm the efficacy and safety of this regimen, and suggest that in some patients response improves during long-term therapy. A detailed and thorough previous history of psoriasis is essential, in order to draw the profile of possible candidates for efalizumab therapy. Patients with a history of unstable types of psoriasis (i.e. erythrodermic psoriasis, pustular and inflammatory lesions), are likely poor responders to efalizumab, and at an increased risk of developing GIF. Further clinical experience is required to verify this observation and to identify other possible prognostic factors for the non-responders.

References

Long-term treatment of plaque psoriasis with efalizumab: an Italian experience

A. Costanzo,* K. Peris,† M. Talamonti,* A. Di Cesare,† M. Concetta Fargnoli,† E. Botti* and S. Chimenti*

*Department of Dermatology, University of Rome ‘Tor Vergata’, Rome, Italy
†Department of Dermatology, University of L’Aquila, L’Aquila, Italy

Summary

Biologic agents are an important new class of drugs, offering targeted treatment for chronic skin diseases such as psoriasis. The biologic therapy efalizumab is an anti-CD11a monoclonal antibody, which was approved by the European regulatory agency in 2004 for the treatment of moderate-to-severe plaque psoriasis. Here we describe our 2-year experience in treating over 100 patients with moderate-to-severe psoriasis with efalizumab at two dermatology centres in Italy. Overall, we found efalizumab is efficacious for a large subset of patients, regardless of previous therapies received, and has an easily manageable safety profile. We believe one important quality of efalizumab is the stability and maintenance of clinical response over time. We found that most patients who respond to treatment experience a long-term clearing of psoriasis with only mild recurrence events. Our experience with individual cases provides specific insights into efalizumab re-treatment, the use of efalizumab in patients with a history of heart failure, and the management of patients who become pregnant or conceive while receiving efalizumab therapy. In summary, our off-trial experience in over 100 patients confirms the efficacy and safety of efalizumab in the treatment of moderate-to-severe plaque psoriasis.

The new class of biologics represents an important weapon in the fight against chronic skin diseases such as psoriasis or psoriatic arthritis.1 The anti-CD11a monoclonal antibody efalizumab is indicated for the treatment of moderate-to-severe plaque psoriasis and was approved by the European Medicines Evaluation Agency (EMEA) in 2004.2 Here, we describe our 2-year experience in treating patients with moderate-to-severe psoriasis with efalizumab.

Patients and methods

We conducted a retrospective analysis evaluating patients treated with efalizumab in the Dermatology Departments at the University of Rome ‘Tor Vergata’ and the University of L’Aquila in Italy. Most of these patients started efalizumab therapy after it had been approved by the EMEA and the Italian regulatory agency, but some of them (10/114) had been involved in a Phase III clinical trial. All patients in the cohort provided written informed consent prior to involvement in this analysis, and were treated according to protocols approved by local ethics committees.

Patients were eligible for efalizumab treatment if they were aged 18–80 years, with at least a 6-month history of plaque psoriasis, and with involvement of at least 10% of total body surface area or a minimum Psoriasis Area and Severity Index (PASI) score of 10. We describe our 2-year experience in treating patients with moderate-to-severe psoriasis with efalizumab.

Accepted for publication
11 January 2007

Key words
efalizumab, Italy, psoriasis, routine clinical practice

Conflicts of interest
AC, SC and KP have acted as paid speakers for Merck Serono*. EB, MT, AC and MCF have declared no conflicts of interest.

*Merck Serono International SA, an affiliate of Merck KGaA, Darmstadt, Germany.
their home by a nurse about drug reconstitution and self-injection technique.

Clinical assessment at baseline included physical examination, vital signs, concomitant medications, Physician’s Global Assessment (PGA) and PASI score. At this visit, we also conducted a complete blood cell count, a lymphocyte count, liver and renal function tests, urine analysis, protein electrophoresis, tests for anti-nuclear antibodies and anti-extractable nuclear antigen antibodies, tests for hepatitis B, hepatitis C and human immunodeficiency viruses, a pregnancy test, a tuberculin test (tine test or purified protein derivative), and a chest X-ray in patients with a positive tuberculin test. After the screening visit, regular clinical and laboratory examinations were performed during treatment at weeks 4, 8 and 12, and then every 2 months thereafter.

The primary endpoint in our analysis was the number of patients achieving a 75% reduction in the PASI score (PASI-75) or a PGA rating of ‘good’ or better, after 12 weeks. A 50% reduction in the PASI score (PASI-50) was our secondary endpoint. Patients who did not achieve PASI-50 or a PGA of good or better at week 12 discontinued efalizumab treatment and were considered to be non-responders. Responding patients were allowed to continue efalizumab treatment until any serious AE (SAE) or a significant loss of efficacy (defined by a loss of at least 50% of the initial PASI score) occurred. Safety and tolerability were assessed by recording the incidence of AEs, documenting any clinically significant changes in laboratory values and also by physical examination.

Efficacy data were analysed using an as-treated approach. The as-treated population included only patients with data available at each visit. It is important to note that patients started treatment at different times, so these data present only a ‘snapshot’ of our experience, taken at the end of May 2006. At this time, many patients had only just started to receive efalizumab treatment. The safety population included all patients who received at least one dose of efalizumab.

### Results

#### Patient characteristics

A total of 114 patients (67 men and 47 women) were eligible for efalizumab treatment. Of these eligible patients, 108 were treated with efalizumab. The remaining six patients refused to initiate the therapy on day 0 because of needle-phobia or for logistical reasons (e.g., difficulties in reaching the dermatology centre for follow-up visits). The mean age of the 114 eligible patients was 44.6 years (range: 22–80 years). Previous treatments included methotrexate, cyclosporin, systemic steroids, phototherapy (UVB and/or PUVA), acitretin, etretinate, etanercept, infliximab and alefacept. Of these, the treatments used most frequently were cyclosporin (74 patients) and acitretin (16 patients).

#### Treatment efficacy

The question asked first and most frequently by patients at the screening visit was: ‘Will this drug work for me?’ Although we cannot predict the clinical response to efalizumab treatment for an individual patient, on the basis of our current knowledge we can certainly give a probability of response. In our cohort, we observed that at week 12, 73% (72/98) of patients had reached PASI-50, 35% (34/98) of patients had achieved PASI-75, and 12% (12/98) of patients were almost clear (PASI-90; Fig. 1). Therefore, at least on the basis of our experience, we can state that a patient attending either of our centres who is eligible for efalizumab treatment has approximately a 70% probability of responding to therapy and is eligible to continue treatment beyond week 12.

![Fig 1. Patients achieving a 50%, 75% or 90% reduction from baseline in Psoriasis Area and Severity Index (PASI) score (PASI-50, 75 and 90, respectively) over time in our patient cohort (as-treated population).](image-url)
Patients reaching PASI-50 at week 12 have a high probability of experiencing further improvement in the subsequent weeks of treatment. In our series, of the patients who had not achieved PASI-75 by week 12 and who had data at week 24, 62% (28/45) of patients achieved PASI-75 by week 24, while 31% (14/45) of patients reached PASI-90 at week 24. In our patients, clinical improvement increased with continuous treatment, reaching a plateau between weeks 24 and 52. After 52 weeks of treatment, 65% (24/37) of patients achieved PASI-75 and 43% (16/37) achieved PASI-90. At week 100, PASI-75 was observed in 67% (6/9) of patients and PASI-90 in 44% (4/9) of patients. Efficacy was maintained in the second year of therapy. Interestingly, the response rate and the drop-out rate we observed in our cohort were very similar to those shown in the placebo-controlled trials.3–5

Safety
Efalizumab treatment was generally well tolerated. AEs were observed in 85% (92/108) of patients (Table 1). Only 12/108 patients discontinued treatment because of an AE; four patients discontinued treatment after the first or the second injection as a result of acute AEs (headache in all cases). Subsequently, we discovered that all of these patients had a history of recurrent headache.

SAEs occurred infrequently (7% of patients; 8/108). All eight patients who experienced a SAE discontinued therapy. Five patients developed a significant inflammatory arthropathy with back pain and joint pain, which occurred within the first 8 weeks of efalizumab treatment. Treatment was discontinued in all of these patients, four of whom were switched to anti-tumour necrosis factor alpha (TNF-α) therapy, with subsequent resolution of the arthropathy. The other patient was treated with nonsteroidal anti-inflammatory drugs, and the arthropathy event resolved. One patient discontinued efalizumab treatment because of severe asthenia. Another patient developed hepatitis E virus-related hepatitis at week 4, caused by water contamination (this case will be analysed in the next section). The eighth patient, a 56-year-old man, experienced aseptic meningitis 7 weeks after starting treatment. This patient presented with a worsening pain, localized at the beginning to shoulder muscles and after 4–5 days also to the neck, with rigidity and headache. The patient was hospitalized and the decision was taken to discontinue efalizumab treatment. A preliminary diagnosis of viral meningitis was made. However, all blood tests for meningitis viruses were negative and the final diagnosis was aseptic meningitis. The event resolved after 15 days of corticosteroid therapy. The patient did not show any neurological consequences and discontinued efalizumab permanently. No clinically significant changes were observed in other haematological values. There was no clinically significant pattern of change in vital signs during efalizumab treatment.

Headache (25%, 27/108), fever (16%, 17/108) and asthenia (13%, 14/108) were the most common acute AEs and occurred most frequently within 48 h of receiving the first two doses of efalizumab, declining steadily in frequency thereafter. Acute AEs were considered mild-to-moderate in severity. This is in line with previous reports.6,7

The incidence of infections during efalizumab therapy was low (14%, 15/108), and comprised pharyngitis, rhinitis and tooth infections. The majority of these cases were considered mild because they did not endanger the patient’s health or require hospitalization.8 Eight patients (7%) experienced a transient, localized, papular eruption (Fig. 2).9 Papular eruption consisted of localized papules and plaques that appeared typically on the flexural areas, neck and face. Histopathologic examination of a papule revealed features compatible with the diagnosis of psoriasis, consisting of focal parakeratosis, collections of neutrophils in the stratum corneum and a dermal infiltrate composed mainly of lymphocytes. Patients who developed a transient papular eruption continued efalizumab therapy and papules cleared. In some patients, we found that adding co-adjvant topical steroid treatment helped to control the eruption.

A total of 19 patients have discontinued efalizumab during the course of their treatment. Of these patients, 12 discontinued because of AEs and seven patients discontinued because of lack of response at week 12.

In the safety population, an increase from baseline in total white blood cell count and a three- to fourfold increase in lymphocyte count were observed during treatment with efalizumab. The increase in lymphocyte count was already statistically significant at week 4 (P < 0.01). The increased white blood cell count was mainly due to the increase in

Table 1 Adverse events (AEs) experienced by patients in the safety population during efalizumab therapy and the number of patients discontinuing treatment due to AEs

<table>
<thead>
<tr>
<th>AEs</th>
<th>Number of patients experiencing AEs (%)</th>
<th>Number of patients discontinuing treatment because of AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27 (25)</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>17 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14 (13)</td>
<td>1</td>
</tr>
<tr>
<td>Transient papular eruption</td>
<td>8 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5 (5)</td>
<td>5</td>
</tr>
<tr>
<td>Tooth infection</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>2 (2)</td>
<td>1</td>
</tr>
<tr>
<td>Flare</td>
<td>2 (2)</td>
<td>2</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis E virus infection</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>92 (85)†</td>
<td>12</td>
</tr>
</tbody>
</table>

*Percentages expressed as a proportion of all patients in the safety population (n = 108). †Patients experiencing at least one AE.
the number of circulating lymphocytes during treatment. However, there was no statistically significant difference in the white blood cell count or the lymphocyte count between responders and non-responders (P > 0.05; data not shown).

There were no deaths during this reporting period.

**Case reports**

We will now describe a few exemplificative cases of patients who we have treated with efalizumab.

**Continuous therapy**

A 65-year-old man presented with a 30-year history of plaque psoriasis. Past medical history included hypertension secondary to cyclosporin therapy. The patient started efalizumab treatment with a baseline PASI score of 16.7. A conditioning dose of 0.7 mg kg\(^{-1}\) was used for the first dose, and each week thereafter, a standard dose of 1 mg kg\(^{-1}\) was administered subcutaneously.

After 12 weeks of efalizumab treatment, this patient achieved PASI-75 (PASI score, 2.7). The patient was continued on efalizumab therapy with further reduction of PASI score and maintenance of PASI-90 after 2 years of continuous therapy (Fig. 3). During efalizumab treatment the patient experienced periodic recurrence of small papules localized to the arms and the trunk; these papules never developed into large plaques but disappeared spontaneously within 3–6 weeks. The patient reached 2 years of continuous therapy and is still receiving treatment. This case illustrates the typical behaviour of psoriasis in a patient who responds to efalizumab.

**Efalizumab re-treatment after a SAE**

A 38-year-old man presented with an 11-year history of moderate-to-severe chronic plaque psoriasis. The patient had no relevant past medical history or concurrent illness and he was not using any concomitant medication. Previous psoriasis therapies included methotrexate and cyclosporin, which were discontinued because of lack of efficacy (methotrexate) or development of hypertension after cyclosporin treatment.

![Fig 2. Clinical appearance of a localized papular eruption in a patient treated with efalizumab.](image)

![Fig 3. Long-term efficacy of efalizumab: clinical improvement in a patient under continuous efalizumab treatment.](image)
The patient was eligible for efalizumab therapy and showed at baseline a PASI score of 15Æ2 (Fig. 4a). The patient responded well to treatment (PASI score, 2Æ4 at week 60). However, after 60 weeks of efalizumab therapy, the patient reported fever, asthenia and jaundice. He was hospitalized and a diagnosis of hepatitis E virus-related hepatitis caused by water contamination was made. Efalizumab treatment was discontinued and the patient referred to our hepatitis centre. His levels of aspartate aminotransferase and alanine aminotransferase returned to normal values in 6 weeks. Twelve weeks after treatment discontinuation, the patient presented with a PASI score of 17Æ7 and was started again on efalizumab.

After 12 weeks of re-treatment with efalizumab, this patient achieved PASI-50 (PASI score, 8Æ4), and after 36 weeks of re-treatment he achieved PASI-75 (PASI score, 1Æ7; Fig. 4b). The patient was continued on efalizumab therapy with further reductions in PASI score and achieved PASI-90 after 48 weeks, showing an excellent response to this second course of therapy, with no further AEs.

### Efalizumab and pregnancy

Reproduction studies have been conducted in mice. The offspring of mice treated with a murine-compatible version of efalizumab demonstrated reduced ability to generate an antibody response for several months after birth. Because a downstream effect was demonstrated in the offspring using this model, efalizumab is rated category C.10

In our clinical experience, four male patients became fathers and three female patients became pregnant while receiving efalizumab treatment. The men were aged 30–48 years, and during the period after the initial 12 weeks of efalizumab treatment all reported that their partners had become pregnant. In all four cases, the pregnancy was regular, with no complications reported at birth or in the first year after birth.

A 33-year-old female patient with a 10-year history of psoriasis was eligible for efalizumab therapy and received the first dose of efalizumab on February 2005. After 4 weeks of therapy she became pregnant and after a further 4 weeks she decided to abort the pregnancy for personal reasons.

A 35-year-old female patient presented with a 17-year history of plaque psoriasis. She had been treated previously with and had responded partially to cyclosporin, systemic retinoids and phototherapy. The patient was started on efalizumab therapy with a baseline PASI score of 7Æ9. After 12 weeks of efalizumab treatment this patient achieved PASI-75 (PASI score, 1Æ7). She was continued on efalizumab therapy, with further reductions in PASI score, and achieved PASI-90 after 28 weeks of continuous therapy. After 52 weeks of efalizumab therapy, she became pregnant and therapy was discontinued. After 2 weeks the patient was hospitalized and a diagnosis of ectopic (fallopian) pregnancy was made. This probably correlated with a congenital malformation of the fallopian tube, and was unlikely to be related to efalizumab treatment. The patient had a spontaneous abortion and the fallopian tube was surgically removed. After 8 weeks of discontinuing efalizumab treatment the patient’s PASI score was 3Æ9. She was started again on efalizumab treatment and after 24 weeks the patient had a PASI score of 0Æ8.

At the present time, a 35-year-old female patient is pregnant. She presented with a 5-year history of moderate-to-severe psoriasis, and previous medications included cyclosporin and systemic retinoids. In December 2005 the patient received the first dose of efalizumab and at week 12 she achieved PASI-90. She continued to receive efalizumab with good control of her psoriasis until week 68 (PASI score, 1Æ2), when the patient discovered she was 7 weeks pregnant and efalizumab treatment was discontinued. Eight weeks after treatment discontinuation, the patient had a PASI score of 0Æ4 and there was no evidence of maternal toxicity, embryo toxicity or teratogenicity.

In summary, we have experienced four healthy newborns fathered by men receiving treatment with efalizumab, and two abortions and one ongoing pregnancy in women who became pregnant while receiving efalizumab.

### Efalizumab and heart failure

Current data regarding efalizumab and heart failure do not exist. In clinical trials, all patients should be screened for a history of heart failure and a physical examination conducted prior to initiation of efalizumab. At our centres, we are...
currently giving efalizumab treatment to two patients with a past medical history of heart failure.

A 59-year-old male had been diagnosed with psoriasis at the age of 49 years. His previous psoriasis treatments included methotrexate and a topical steroid. The patient’s medical history included heart failure in 1998 and allergy to walnuts in 1987. He was receiving enalapril, 20 mg daily, acetylsalicylic acid, 1.5 mg daily, carvedilol, 6.25 mg daily, and latanoprost, 0.001 mg daily. The patient was started on efalizumab therapy with a baseline PASI score of 12.9 in November 2005. After 12 weeks of efalizumab treatment, the patient did not achieve PASI-50 (PASI score, 9.12 weeks of efalizumab treatment, the patient achieved PASI-50 (PASI score, 4) in November 2005. After 12 weeks of efalizumab treatment, the patient showed no evidence of changes in cardiac function during efalizumab therapy.

A 55-year-old male had been diagnosed with psoriasis at the age of 49 years. His previous psoriasis treatments included methotrexate and a topical steroid. The patient’s medical history included heart failure in 1981, glaucoma in 2000 and stable angina pectoris from 2003. The patient was classified as New York Heart Association (NYHA) class III. His medications were carvedilol, 6.25 mg daily, acetylsalicylic acid, 150 mg daily, and latanoprost, 1.5 mg daily. The patient was started on efalizumab therapy with a baseline PASI score of 12.9 in November 2005. After 12 weeks of efalizumab treatment, the patient achieved PASI-50 (PASI score, 4) and he continued to receive efalizumab with good control of his psoriasis after 32 weeks of continuous therapy. Cardiologic follow up showed no evidence of changes in cardiac function during efalizumab therapy.

Discussion

Targeted biologic therapies represent the most advanced kind of treatment for psoriasis. The efficacy and safety of efalizumab have been demonstrated both in clinical trials and in several years of off-trial experience in the USA. European dermatologists have been allowed to prescribe efalizumab since 2004.

Here we have described our experience in the treatment of plaque psoriasis with efalizumab. It is worth noting that this was a retrospective analysis providing a snapshot of a relatively small patient cohort, and only a few data were available for later time points as many patients had not yet reached this duration of treatment when we performed the analysis. Nevertheless, the overall impression we have gained is of a drug that is efficacious for a large subset of patients (over 70% achieve PASI-50 after 12 weeks of treatment), regardless of previous therapies received, and has an easily manageable safety profile.

An important advantage of efalizumab over other biologic drugs is the stability and maintenance of clinical response over time. We found that most responding patients experience a long-term clearing of psoriasis with only mild recurrence events, as shown in the first case report described in this paper. In our experience, discontinuation of efalizumab does not preclude the possibility of achieving a good response in a second course of therapy. Our second clinical case describes a patient discontinuing treatment because of an SAE unrelated to efalizumab, who showed an optimal response to the second course of treatment.

We believe that the critical step in the clinical management of efalizumab is to determine who will benefit from this therapy as soon as possible. This step allows therapy to be continued beyond the 12-week decision point only in patients who will benefit from efalizumab, and also allows ‘non-responding’ patients to be switched to alternative treatments. Unfortunately, simple laboratory tests do not help in determining responsiveness to efalizumab. For example, lymphocyte count has been linked to the molecular mechanism of action of efalizumab. However, in our patients we have not observed any significant difference in the number of peripheral lymphocytes between responding and non-responding patients. This highlights further the importance of clinical improvements in psoriasis lesions as the principal measure of treatment response.

Thus, we agree with the widely accepted opinion that PASI-50 at week 12 is the principal measure to use when deciding whether or not to continue efalizumab treatment. However, we have also observed that patients who fail to reach PASI-50 at week 12, but who show a progressive clinical improvement in the first period of treatment, may benefit from long-term efalizumab therapy and display a good response profile over time. In our experience, these patients continue to improve and almost all of them reached PASI-75 between weeks 24 and 48.

A typical responding patient may experience recurrences of psoriasis symptoms during efalizumab therapy. These can occur in the clinical form of popular reaction or as small plaques; these eruptions regress spontaneously within 2 weeks but they can also be controlled easily with topical therapy.

In our experience, efalizumab has an optimal safety profile. The most frequent side-effect we have observed is flu-like syndrome, occurring within 48 h of the first or the second injection. Four patients discontinued efalizumab because of a strong headache after the first or second dose of efalizumab, but all of these patients had suffered previously from frequent headaches. This suggests that when considering efalizumab as a potential therapy, patient history should include information about previous headaches. In patients with a history of headache, a preventive analgesic therapy may be useful to minimize the risk of headache if efalizumab therapy is started.

Although we advise patients to avoid pregnancy while receiving efalizumab, we have experienced seven patients who have become pregnant or fathered a child during efalizumab treatment. All four children fathered by men receiving efalizumab were healthy, with no malformations and no major health problems reported to date. Efalizumab was not discontinued in any of these patients. Only one of three women who became pregnant while receiving efalizumab is...
continuing her pregnancy. The other two women underwent either voluntary or spontaneous abortion (considered unrelated to treatment). Efalizumab was discontinued in all three of these women as soon as the pregnancy was communicated. Although limited to few cases, our observations suggest that efalizumab does not represent a major problem for male fertility.

Studies on co-morbidity indicate that moderate-to-severe psoriasis may be associated with hyperlipidaemia and atherosclerosis. These factors are frequently linked to heart failure. Psoriasis patients with a history of heart failure are not infrequent. How do we manage these patients? Is it safe to administer a systemic drug for psoriasis in these patients? Cyclosporin is, of course, contraindicated because of its effects on blood pressure and renal function. In contrast, it has been suggested that some anti-TNF-α biologic therapies (infliximab and etanercept) may actually help to prevent heart failure. However, clinical trials designed to investigate the efficacy of infliximab for the treatment of heart failure were discontinued because of lack of efficacy and an increase in death rate. We have administered efalizumab for the treatment of psoriasis in two patients affected by severe psoriasis and postischaemic heart failure. Both patients experienced an improvement in psoriasis with efalizumab treatment. Treatment showed no effect on their cardiac function after 3 and 9 months of therapy.

In conclusion, our off-trial experience in over 100 patients confirms the efficacy and safety of efalizumab in the treatment of moderate-to-severe plaque psoriasis. Furthermore, our experience with individual cases provides additional information about efalizumab re-treatment, the use of efalizumab in patients with a history of heart failure, and the management of patients who become pregnant or conceive while receiving efalizumab therapy.

References
Managing moderate-to-severe psoriasis with efalizumab: experience at a single Spanish institute
C. Ferrándiz and J.M. Carrascosa
Hospital Universitario Germans Trias i Pujol, Badalona, Universidad Autónoma de Barcelona, Spain

Summary
Psoriasis is a lifelong, incurable disease that normally develops before the age of 30 years and affects approximately 1·4% of the Spanish population. Numerous clinical trials have demonstrated the efficacy of efalizumab, a recombinant, humanized, monoclonal antibody, which has been approved for the treatment of moderate-to-severe plaque psoriasis. However, clinical trials do not necessarily reflect routine clinical practice because they are conducted under controlled conditions and in specific populations. In this paper, we describe our experiences at a large University Hospital in Spain using efalizumab to manage patients with psoriasis. We found that patients who respond to treatment at week 12 usually demonstrate long-term disease control with continuous use of efalizumab. Early response may be easiest to achieve in patients with extensive body surface area (BSA) involvement and low Psoriasis Area and Severity Index (PASI) scores for erythema, induration and desquamation. However, evaluation of treatment success after 12 weeks may be premature in patients with moderate or low BSA involvement if they have clinically significant PASI scores for erythema, induration and desquamation. In our experience, the safety profile is good and patients appreciate the convenience of efalizumab compared with other interventions.

Selecting patients for efalizumab treatment
Although biologics can be used as first-line therapy in the treatment of moderate-to-severe psoriasis,11,12 all patients attending our centre are assessed to ensure that they meet all the criteria required by the European Medicines Evaluation Agency for therapy with efalizumab: adult patients with moderate-to-severe chronic plaque psoriasis who have failed to respond to, or have a contraindication to, or are intolerant to other systemic therapies, including cyclosporin, methotrexate (MTX) and psoralen ultraviolet-A (PUVA). Other factors are also considered when making the decision to treat patients...
with efalizumab: are they ‘heavy drinker’ patients who are without hepatic disease? Do they have hypertension or bad therapeutic compliance? Are they unable to travel to the hospital 2–3 times every week to receive phototherapy?

To avoid treating patients who are contraindicated against efalizumab, we then identify the patients who have a history of internal malignancy or melanoma, or opportunistic or clinically significant recurrent infections, women who are pregnant, breastfeeding or trying to become pregnant, and patients with moderate-to-severe arthritis.

The third step is a general physical examination, which is conducted to exclude the possibility of organomegaly, adenopathy and nonmelanoma skin cancer (although we do not consider this latter condition to be a contraindication for efalizumab treatment).

The fourth step includes routine haematological and biochemical tests and a chest X-ray – this is performed due to the high prevalence of tuberculosis in Spain, but is not mandatory in most guidelines. It is cheap and easy to perform and allows the presence of silent lung neoplasia or tuberculosis infection to be ruled out. Indeed, it is worth commenting that, in one patient, we incidentally detected a lung neoplasia when assessing their suitability for treatment with efalizumab.

Finally, we set aside time to ensure that patients understand how to self-administer the drug and have realistic expectations (e.g. success rates, onset of action and safety), so that they understand the possible short- and long-term side-effects and appreciate the need for monitoring as well as attending the scheduled visits during the coming months of treatment. We also emphasize the importance of immediately reporting any significant change in the disease state to their physician. We have found that once this has been discussed, patients do appreciate the convenience of the once-a-week dose of efalizumab, as well as the reduced number of medical appointments and biochemical assessments compared with alternative treatments. This is particularly true for people who have an ‘active working life’. Generally, patients agree to start on efalizumab treatment following our discussions.

From a general epidemiological point of view, it is interesting to note that 80% of the patients we have treated with efalizumab were aged between 20 and 55 years and were considered to be relatively healthy. This may be because we tended to avoid treating individuals who were older than 55 years or who had significant associated co-morbidity. We felt that this approach was prudent when managing psoriasis using a new drug and may also reduce the incidence of secondary effects, which may increase when less suitable groups of patients are included.

Evaluating efficacy

Although efalizumab has a rapid onset of action in many patients, response to treatment should be formally assessed 12 weeks after initiation. At this point, we have found that 67% (18/27 patients) of efalizumab-treated patients at our centre achieved a Psoriasis Area and Severity (PASI)-50 improvement or better and 43% of these patients reached a PASI-75 response, with a 60% overall reduction in PASI score. The proportions of patients achieving PASI-50 and PASI-75 score at our centre are higher than for other clinical trials.13

In our experience, there are two broad categories of responders: ‘slow responders’ and ‘quick responders’. The first one generally represents those patients suffering from moderate psoriasis (as measured on the PASI) and relatively few lesions [low body surface area (BSA) involvement] but a high overall lesion severity (OLS) score. Typically, psoriasis continues to improve after week 12 in these patients and they are able to achieve an almost clear status on the Physician’s Global Assessment scale at weeks 20–24. This was the case for a 46-year-old woman with long-standing psoriasis. She had been treated previously with MTX, which was stopped because of epigastralgia, and then she received phototherapy [PUVA and ultraviolet-B (UVB)] for several months. In addition, she had previously received efalizumab for 12 weeks during a clinical trial, which had resulted in a significant but incomplete resolution of cutaneous lesions. A few months later, we decided to restart efalizumab – PASI score fell from 14 at initiation of treatment to 4 at week 12. At this point, we decided to continue therapy with efalizumab and, by week 28, the patient had achieved a PASI score of nearly zero.

‘Quick responders’ are generally those patients with a moderate PASI score and a moderate-to-low OLS score, but with extensive BSA involvement. Typically, these patients experience a rapid improvement in PASI score. As an example, we report the case of a 42-year-old man who had been treated previously with PUVA, re-PUVA, narrow-band UVB (NBUVB) and MTX, but who had an irregular or transitory response and intolerance to some of these treatments. Satisfactory clinical resolution was observed within 3 weeks, with PASI score dropping from 24 to 14 during this period. At week 12, this patient had achieved a PASI score of 4. After stopping therapy, disease recurred by 4 weeks. Consequently, efalizumab treatment was restarted and the patient had a comparable response and tolerance to treatment as that obtained on the first course. Currently, this patient is being given continuous efalizumab therapy for 36 weeks.

Thus, based on our experience, patients with extensive BSA involvement and low OLS scores respond quickly to efalizumab treatment and have a good clinical prognosis – remission may be easier to achieve in these patients. Conversely, patients with a moderate BSA involvement but a significant OLS score may take longer than 12 weeks to achieve a significant improvement in PASI score.

A point that merits some comment is the peculiar lesion response observed in some patients on efalizumab treatment. These patients demonstrate an annular evolution of lesions that initially start clearing from the centre, but persist at the periphery (Fig. 1). This is usually a transitory state that often occurs after 4–8 weeks of efalizumab treatment. Subsequently, the periphery of these lesions will also often clear and the lesion will resolve completely, although this process occurs more slowly.
Continuous versus intermittent therapy

When we first started using efalizumab in our daily clinical practice, we would stop treatment when patients achieved a PASI-75 response or after 12 weeks to evaluate the period of remission. In our experience, a progressive recurrence was experienced by most patients, often 4–8 weeks after stopping therapy. This also happens with any other systemic therapy and has been observed in clinical trials. We have found that efalizumab re-treatment is effective and well tolerated in patients with a recurrence of psoriasis, as reported previously. However, in a very small proportion of patients, PASI score at recurrence is somewhat higher than before therapy, but re-treatment was also effective for some weeks.

An illustrative example of a patient for whom efalizumab re-treatment was effective and well tolerated is that of a 39-year-old male with a 20-year history of psoriasis. This patient had a baseline BSA of 60% and originally received efalizumab treatment while participating in a clinical trial. After 12 weeks of treatment his psoriatic plaques had almost cleared, with a BSA of 5%. However, at this point efalizumab was discontinued, as scheduled by the study protocol, and a relapse was seen after 4 weeks (Fig. 2a, b). In subsequent months, efalizumab was re-introduced and stopped twice, after 3 and 6 months, for protocol requirement and personal reasons, respectively. In both cases clinical response as well as relapse were similar to those observed after the first course (Fig. 2c, d). Finally, the patient re-started efalizumab again with near complete clearance, which was still maintained after 8 months of continuous therapy. No adverse events were detected during any of the courses of efalizumab treatment.

As patients often have recurrence of psoriasis after stopping efalizumab treatment, which may have a negative psychological impact on patients, we believe that continuous therapy is always a better option than intermittent therapy – this is our preference at the present time. Also, it could be argued that intermittent therapy may not be the most sensible course of action when treating a chronic disease, as is the case of psoriasis.

When we are faced with patients who do not respond to efalizumab treatment (<50% improvement in PASI score), we prefer to discontinue therapy at week 12, but we start concomitant treatment with a systemic agent for at least 4 weeks, to give the new agent an opportunity to reach maximal effect before efalizumab treatment is stopped. The aim of this approach is to avoid worsening of psoriasis, or even rebound, after stopping efalizumab therapy.

Safety

In this section, we consider two different classes of adverse event: those that are not related to psoriasis and those that are.

Fig 1. Unusual annular evolution of a lesion that has cleared from the centre, but persisted at the periphery.

Fig 2. (a, b) Relapse after discontinuation of efalizumab and (c, d) re-treatment resulting in near complete clearance of psoriasis after 8 months of continuous therapy.
Adverse events not related to psoriasis

Nearly half of the patients we have treated with efalizumab have experienced flu-like symptoms, which typically occur 8–24 hours after the first injection and last for some hours. They consisted primarily of myalgia, headache, chills and nausea. Fever was reported by only one patient. All patients reported these acute adverse events as mild and, in most cases, limited to the first two doses. None of the patients at our centre discontinued efalizumab treatment because of flu-like symptoms. Because patients have been educated about the possibility of flu-like symptoms, we have found that patients at our centre do not consider the appearance of these symptoms as a reason for an extra visit.

At our centre, two cases of bacterial cellulites have been reported: one case in the right ear of a 57-year-old man after the fourth dose of efalizumab and the other in the right leg of a 45-year-old obese woman at the eighth injection. In both cases a good response to antibiotics was obtained and efalizumab treatment did not need to be discontinued. After many months of efalizumab treatment, neither patient has presented with any other infection.

The relationship between efalizumab therapy and infection is difficult to establish, and long-term trials have shown no increased risk of infection.8,13 Also, incidental occurrence of infections that are not related to efalizumab therapy cannot be ruled out. We have not registered any cases of malignancy, thrombocytopenia, anaemia or joint-related symptoms at our centre during treatment with efalizumab. Frequently, cases of mild leukocytosis with lymphocytosis, as a natural consequence of the mechanism of action of efalizumab, have been recorded. This finding was irrelevant from a clinical point of view.

Psoriasis-related adverse events

At our centre, two patients developed a peculiar eruption after 8–12 injections of efalizumab, which fulfilled the criteria for localized mild breakthrough, or transient localized papular eruption.15 These consisted of a papular eruption on the trunk localized mild breakthrough, or transient localized papular eruption.15 At our centre, two patients developed a peculiar eruption after 8–12 injections of efalizumab, which fulfilled the criteria for localized mild breakthrough, or transient localized papular eruption.15 At our centre, two patients developed a peculiar eruption after 8–12 injections of efalizumab, which fulfilled the criteria for localized mild breakthrough, or transient localized papular eruption.15 These consisted of a papular eruption on the trunk localized mild breakthrough, or transient localized papular eruption.15 At our centre, two patients developed a peculiar eruption after 8–12 injections of efalizumab, which fulfilled the criteria for localized mild breakthrough, or transient localized papular eruption.15 These consisted of a papular eruption on the trunk localized mild breakthrough, or transient localized papular eruption.15 At our centre, two patients developed a peculiar eruption after 8–12 injections of efalizumab, which fulfilled the criteria for localized mild breakthrough, or transient localized papular eruption.15 These consisted of a papular eruption on the trunk localized mild breakthrough, or transient localized papular eruption.15 At our centre, two patients developed a peculiar eruption after 8–12 injections of efalizumab, which fulfilled the criteria for localized mild breakthrough, or transient localized papular eruption.15 These consisted of a papular eruption on the trunk localized mild breakthrough, or transient localized papular eruption.15 At our centre, two patients developed a peculiar eruption after 8–12 injections of efalizumab, which fulfilled the criteria for localized mild breakthrough, or transient localized papular eruption.15 These consisted of a papular eruption on the trunk localized mild breakthrough, or transient localized papular eruption.15 At our centre, two patients developed a peculiar eruption after 8–12 injections of efalizumab, which fulfilled the criteria for localized mild breakthrough, or transient localized papular eruption.15

Fig 3. Generalized inflammatory flare (a) during efalizumab treatment and (b) response after nine concomitant sessions of narrow-band ultraviolet-B treatment.
failure of efalizumab to control the disease. Nevertheless, as observed at our centre and reported previously, clinical fluctuations in psoriasis during therapy with efalizumab may be managed by the temporary addition of an anti-psoriatic therapy. This seems to be particularly useful in patients receiving continuous treatment with efalizumab who have previously shown good response — this was the case for the patient at our centre. We decided to add NBUVB, as this is considered among the most effective treatments for severe psoriasis. In addition, NBUVB is usually well tolerated and has not been related to end-organ toxicity. However, it could be hypothesized that apoptotic effects of NBUVB therapy on T lymphocytes, as well as immunosuppressive effects on the cutaneous microenvironment, may work in a synergistic way with the effects of efalizumab on T cell activation, cutaneous T cell trafficking, and T cell adhesion to keratinocytes.

Thus, the development of GIF during efalizumab therapy does not always indicate a loss of responsiveness to efalizumab. Therefore, several factors, such as the natural fluctuation in the course of the disease and the existence of the possible triggering factors, should be taken into consideration before discontinuing treatment. If GIF occurs during efalizumab therapy but does not resolve following the temporary (4 weeks) addition of an anti-psoriatic therapy, efalizumab must be discontinued and the patient transitioned to an alternative systemic therapy.

In addition to the cases highlighted already, we have also observed some patients who had mild ‘worsening’ of psoriasis during efalizumab therapy; these patients were well controlled with topical steroids.

Efalizumab therapy in patients with localized psoriasis

As stated already, efalizumab is approved for moderate-to-severe chronic plaque psoriasis. However, we have found that there are some types of psoriasis that, although limited in extent and severity in terms PASI score, can be highly disabling and have a dramatic impact on quality of life. Consequently, we feel that these types should be managed in the same way as severe psoriasis. In particular, this applies to some patients with recalcitrant nonpustular palmoplantar psoriasis. Indeed, we would argue that systemic therapies may be beneficial, even though such treatments are not indicated in these patients. We have treated two such patients with efalizumab and had varying degrees of success.

A good response to treatment was obtained in a 55-year-old woman with a 9-year history of nonpustular palmoplantar psoriasis who had very mild, occasional plaque involvement on the elbows and knees. After showing only a partial response to topical PUVA and a failure to respond to MTX, efalizumab was started at 1 mg kg⁻¹ per week. After 5 weeks of efalizumab treatment, the plaque psoriasis on the patient’s hands and feet was reduced by 50% and, by week 12, her symptoms were resolved completely. The patient continued to receive efalizumab and remained lesion free. Unfortunately, in September 2006 after 6 months of continuous efalizumab treatment, the patient developed thrombocytopenia and treatment was discontinued. This rare side-effect has been reported in 0-3% of patients during clinical trials with efalizumab.

Because of our initially positive experiences with this patient, we initiated efalizumab treatment in a patient with pustular palmoplantar psoriasis who, previously, had been partially controlled with cyclosporin at high doses. However, progressive tapering of cyclosporin overlapping with initiation of efalizumab was accompanied by an exacerbation of psoriasis and the appearance of new pustules, as well as deep palmar fissures. Consequently, the patient decided to discontinue efalizumab.

Can non-responders to efalizumab be characterized?

In order to optimize efalizumab therapy and to avoid unsuccessful outcomes, it is important to know the profile of patients who may not respond well to first-line treatment with efalizumab. Like other anti-psoriatic treatments, the response to efalizumab is not uniform among patients. This may be due to the unpredictable and fluctuating severity of the disease, as well as the genetic predisposition of patients. Therefore, it is very important to accurately select suitable candidates for efalizumab treatment.

Before initiating efalizumab treatment, we have found that it is important to establish that the patient does not have a history of unstable psoriasis or pustular psoriatic flares, as treatment may result in worsening or exacerbation of psoriasis. An example of this was a 36-year-old man with a history of unstable and difficult to manage psoriasis characterized by frequent acute flares of intense erythematous psoriatic plaques, sometimes accompanied by pustules. He had received cyclosporin for 6 years, which was stopped because of hypertension as well as renal function deterioration. PUVA and UVB had been tolerated badly or did not control the disease. Because of this, we decided to initiate efalizumab 2 weeks before discontinuing NBUVB treatment. After 12 weeks of efalizumab treatment, the patient’s PASI score deteriorated from 21 at initiation to 27, and new inflammatory and erythematous plaques and pustular lesions developed in new, previously unaffected locations. The patient decided to stop efalizumab treatment. Accordingly, we do not tend to prescribe efalizumab as the first-line treatment in patients with unstable, inflammatory psoriasis with the presence of pustules. However, more studies need to be conducted in this subgroup of patients before it can be confirmed that these features are accurate markers of failure to efalizumab therapy.

Conclusions

Efalizumab therapy for moderate-to-severe chronic plaque psoriasis provides safe, long-term control of psoriatic symptoms in a significant proportion of patients.

In our experience, patients who respond to treatment at week 12 usually demonstrate constant long-term disease control with the continuous use of efalizumab. The safety profile...
is good and patients appreciate the convenience of efalizumab compared with other interventions.

From a practical point of view, it would be desirable to characterize the clinical profile of patients who respond well to efalizumab treatment and who experience continuous symptom control such that unnecessary treatment of patients who are likely to be non-responders is avoided.

In our experience, clinical outcomes to treatment are best and most rapid in patients who have stable psoriasis. Also, early response may be easiest to achieve in patients with extensive BSA involvement and low PASI scores for erythema, induration and desquamation. However, evaluation of treatment success after 12 weeks of efalizumab therapy may be premature in patients with moderate, or even low, BSA involvement who have clinically significant PASI scores for erythema, induration and desquamation, because it can take more than 12 weeks to achieve a significant response. We have found, therefore, that it is essential to educate patients about the different possibilities for their response to treatment in order to maximize adherence.

In patients with severe psoriasis who respond to treatment with efalizumab, clinical fluctuations during continuous therapy are rare and can usually be controlled by the temporary addition of anti-psoriatic therapies. However, a concerted effort is necessary to evaluate which conventional therapies are most effective for this temporary control of disease flares.

When educating patients, particular emphasis should be placed on recognizing and reporting psoriasis-related adverse events during, or after, efalizumab treatment – we have found these events are most prevalent in nonresponders. Patients should be encouraged to contact their physician immediately in order to minimize the impact of these events. Also, it is important to emphasize that patients who have responded favourably to efalizumab, but who have discontinued treatment through choice, can restart at any time and are likely to achieve similar success to that obtained after the first treatment. Furthermore, the dramatic efficacy of efalizumab in the patient we treated for recalcitrant nonpustular palmoplantar psoriasis may suggest that the indication for efalizumab could usefully be expanded to include this focal but disabling condition; however, more studies are needed to confirm this.

References


