

Efalizumab

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ABSTRACT: Efalizumab is a novel immunomodulator that blocks T-cell migration and activation. The drug was initially approved in October 2003 for the treatment of adult patients with chronic moderate to severe plaque psoriasis. This review will discuss the efficacy and safety data for efalizumab in the treatment of psoriasis. In clinical use, efalizumab has utility as a first-line biologic therapy for plaque psoriasis, as well as a first-line choice for hand and foot psoriasis, overweight patients, and those who have had inadequate response to a TNF inhibitor. In addition, several off-label applications of efalizumab will be reviewed.

KEYWORDS: biologic, efalizumab, immune modulators, psoriasis

Efalizumab is a recombinant monoclonal antibody that binds to CD11a, a subunit of leukocyte function antigen-1 (LFA-1). LFA-1 is a T-cell surface molecule important in T cell activation, T-cell migration into skin, and cytotoxic T-cell function. By binding to CD 11a, the drug blocks the interaction between LFA-1 and ICAM-1, the molecule found on vascular endothelium responsible for adhesion. Therefore, the drug prevents migration of T cells out of the peripheral blood vessels and into the skin. This blockade is reversible and does not diminish T cells. The drug is administered subcutaneously once weekly.

On-label use of efalizumab

Psoriasis

Efalizumab is FDA approved for the treatment of psoriasis. A phase III trial with weekly subcutaneous injection showed promising results in the treatment of moderate to severe plaque psoriasis (1). The multicenter, randomized, placebo-controlled, double-blind study consisted of 597 subjects who either received 1 mg/kg/week, 2 mg/kg/week, or

placebo. Depending on response after 12 weeks, subjects received an additional 12 weeks of treatment of efalizumab or placebo. The treatment was stopped at week 24 and subjects were followed up for another 12 weeks.

By week 12, there was an improvement of 75% or more in the psoriasis area severity index (PASI) in 22% of subjects with 1 mg/kg/week dosing and 28% with 2 mg/kg/week dosing. However, only 5% of subjects showed such improvement in the placebo group. Significant differences between placebo and treatment groups were seen as early as week 4. Of those patients that had 75% or more improvement by week 12, improvement was maintained through week 24 in 77% of subjects who received efalizumab, compared with 20% of those who were then switched to placebo ($p < 0.001$).

At week 24, all patients stopped use of efalizumab. Thirty percent of patients maintained an improvement of 50% or more in the PASI upon follow-up 12 weeks later. Patients tolerated the drug well, and adverse events were mild to moderate. The authors concluded that subjects with moderate to severe plaque psoriasis treated with efalizumab experienced significant improvement. Furthermore, prolonging the course of treatment from 12 to 24 weeks resulted in both maintenance and improvement of responses.

In another phase III trial (randomized, double-blind, parallel-group, placebo-controlled), Gordon et al. (2) assessed the efficacy and safety of efalizumab in patients with plaque psoriasis. They enrolled 556 adults with stable, moderate to severe

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plaque psoriasis in 30 study centers in the United States and Canada between January and July of 2002. The patients were randomly assigned: two-thirds of patients ($n = 369$) received 12 weekly doses (1 mg/kg) of subcutaneous efalizumab whereas the last third ($n = 187$) received placebo. The authors used the following as end-points: at least 75% improvement in the PASI, improvement on the overall dermatology life quality index (DLQI), itching visual analog scale (VAS), and psoriasis symptom assessment (PSA) at 12 weeks versus baseline.

Subjects who received efalizumab had significantly greater improvement in all of the above end-points compared with those who received placebo. Twenty-seven percent of subjects treatment with efalizumab achieved PASI 75, whereas only 4% of those on placebo achieved the same result. Efalizumab-treated patients exhibited a greater mean percentage improvement than placebo treated patients on the overall DLQI (47% vs. 14%, $p < 0.001$), itching VAS (38% vs. -0.02%, $p < 0.001$), and PSA frequency and severity subscales (48 vs. 18% and 47 vs. 17%, respectively, $p < 0.001$). Again, efalizumab was found to be safe and well tolerated, and adverse events were mild to moderate.

Safety

Side effects with efalizumab are generally rare. Many patients complain of chills, fever, headache, myalgia, and/or nausea that occur within 2 days of the first injection (29%). A lower, conditioning dose is recommended to reduce the incidence and severity of first dose reactions. Other common side effects include lymphocytosis (40%), leukocytosis (26%), and infection (29%). The risk of serious infection is very low ($< 1\%$); however, the drug should be avoided in those with chronic infection, history of recurrent infections and the elderly (1).

The product labeling for efalizumab includes cautions about a potential increased risk of infection and malignancy, but an increase in the risk of either of these conditions has not been clearly demonstrated in either clinical trials or postmarketing surveillance. There have been no opportunistic infections, no clinical signs of immunosuppression, and no hepatotoxicity or nephrotoxicity associated with the use of efalizumab (3). In the phase III trial, there was no evidence of T-cell depletion or increased risk of end-organ toxicity, malignancy, or infection (1).

Efalizumab is very well tolerated, and the only significant safety concern is the risk of psoriasis worsening during or after discontinuation of therapy. In clinical trials, 14% of efalizumab-treated

subjects who were abruptly withdrawn from treatment experienced an increase in the severity of their psoriasis to a worse degree than it had been at baseline (rebound) (4). Rebound following efalizumab discontinuation was much more likely to occur in patients who did not respond well to efalizumab, but it can occur in treatment responders as well. A further minor safety concern during efalizumab therapy is the incidence of thrombocytopenia and hemolytic anemia. During clinical trials for efalizumab, a small number of patients (8/2762; 0.3%) experienced reversible thrombocytopenia (4). The causal relationship between efalizumab therapy and thrombocytopenia is unknown, but the product labeling recommends that platelet counts be obtained monthly for the first 3 months of efalizumab treatment, and every 3 months thereafter (4). Thrombocytopenia and hemolytic anemia are very rare, but treatment should be discontinued if such events occur. In addition, a small number of patients experience flare of their psoriasis while on therapy (5). In addition to a flare of psoriasis that might occur in some patients, there have been reports of patients whose psoriasis seemingly changed character during therapy. Some cases of inverse psoriasis and some of pustular psoriasis have been reported. The practitioner should be prepared to deal with such patients and should be able to use therapies such as ultraviolet light, methotrexate, acetrelin, or cyclosporine, at least temporarily.

Hand and foot psoriasis

Over the past several years, there have been many anecdotal observations of the efficacy of efalizumab in the treatment of hand and foot psoriasis. Fretzin et al. (6) recently reviewed the cases of 17 patients who were treated with efalizumab for hand and foot psoriasis.

Efalizumab acted rapidly with most patients achieving clearance of their disease in less than three months, and treatment was well tolerated. Many of these patients had physical limitations from their disease, and efalizumab treatment allowed them to resume their normal activities of daily life (6). The authors concluded that the efficacy of efalizumab in treating these cases of hand and foot psoriasis suggests that it may provide therapeutic benefit.

Recently, Leonardi et al. (7) presented the results of a phase IV randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of efalizumab in patients with chronic moderate to severe plaque psoriasis involving the hands and/or feet. Patients with psoriasis on other

areas of the body were also eligible for this study, so long as they had plaque psoriasis (with or without pustules) that involved the hands and/or feet.

In this randomized, placebo-controlled clinical trial, 46.2% of patients with chronic moderate to severe plaque psoriasis involving the hands and/or feet achieved PGA scores of clear (0), almost clear (1), or mild (2) after 12 weeks of efalizumab therapy. In the placebo group, 17.9% of patients achieved PGA score of clear, almost clear, or mild ($p=0.015$). One-third (32.7%) of patients who received efalizumab achieved a PGA rating of clear (0) or almost clear (1) after 12 weeks of efalizumab therapy (versus 7.1% in the placebo group; $p=0.013$). The incidence of adverse events in patients treated with efalizumab was similar with those treated with placebo and was consistent with the safety profile observed in the phase III studies. The results of this trial further validate a large number of published case reports where efalizumab treatment is effective in this often recalcitrant and hard to treat patient population (7).

Practical use

In the present authors' practice, efalizumab is an important treatment for moderate to severe psoriasis. The drug offers the benefit of efficacy and safety. In the first year of therapy, a small number of patients experienced instability of their psoriasis in the form of a localized mild breakthrough or, more rarely, a generalized inflammatory flare. By 6 to 12 months, these events become very infrequent, and most patients who respond tend to maintain a stable response. The incidence of major systemic side effects is quite small.

In clinical use, efalizumab has utility as a first-line biologic therapy for psoriasis, as well as a first-line choice for hand and foot psoriasis, overweight patients, and those who have had inadequate response to a TNF-inhibitor.

Efalizumab is the only biologic studied continuously in a 36-month trial (8). The efficacy of efalizumab was maintained throughout 36 months of continuous treatment based on the ITT analysis ($n=339$ for all treatment segments). After the first 3 months of therapy, 41.3% of all patients ($n=339$) had achieved PASI 75 and 13.0% achieved a PASI 90.

After completion of the maintenance treatment period (month 33), response rates were 47.2% PASI 75 and 26.8% PASI 90. Patients were transitioned out of the study after month 33. After completion of the transition treatment period (month 36), response rates were 45.4% PASI 75 and 24.5% PASI 90. This represents the longest continuous treatment to

date for any biologic therapy in a clinical trial for psoriasis. There was no increase over time in the overall incidence of adverse events, no emergence of new common adverse events, no apparent trend toward an increase in the incidence of clinically significant adverse events, and no evidence of cumulative or end-organ toxicity. Results of this 36-month study support the long-term efficacy and safety profiles of efalizumab in patients with moderate to severe chronic plaque psoriasis.

Recent data have indicated that efalizumab may have utility for overweight patients (9). Efalizumab dosing is weight-based. A pooled analysis of three placebo-controlled, randomized phase III clinical studies with efalizumab showed consistent response across all weight and body mass index groups who had undergone 12 and 24 weeks of treatment (9). An analysis of patient response in relation to patient weight was performed in the 3-year open-label phase III clinical study and indicated a consistent response for both heavy (91 kg) and nonheavy (<91 kg) patients throughout the term of the study.

For patients with an inadequate response to TNF-inhibitors, efalizumab may be a therapeutic option. This drug offers a different mechanism of action and therefore may be of benefit. A phase IV study is currently underway to assess the efficacy of efalizumab in individuals with inadequate response to a TNF inhibitor.

Off-label use of efalizumab

Atopic dermatitis

Severe atopic dermatitis (AD) often cannot be controlled with topical agents. The use of current systemic therapies such as oral corticosteroids, azathioprine, and methotrexate, poses the risk of serious adverse events. Chronic use of any of these invariably causes end-organ toxicities.

Weinberg and Siegfried (10) reported successful treatment of severe atopic dermatitis in a child and an adult with efalizumab. A pertinent clinical observation is that both patients experienced gradual rather than abrupt improvement over 3–6 months of efalizumab treatment. The pediatric patient began to experience improvement after 2 months of therapy, with almost complete clearing by 6 months. The adult patient did not begin to show significant improvement until after 6 months of therapy. This gradual response may have been attributable to the severity of their disease or to the time required for efalizumab to correct the pathophysiologic conditions (10).

In an investigator-initiated, prospective, open-label, pilot study, 10 patients with severe AD received an initial conditioning dose of 0.7 mg/kg followed by 1 mg/kg weekly for another 11 weeks (11). Efficacy was measured based on a change in the mean eczema area and severity index (EASI) from baseline after the 12 weekly doses. Patients were monitored out to week 20 to assess for adverse events after discontinuation of therapy. EASI scores improved from a mean baseline score of 37.1 ± 13.5 to 17.6 ± 14.5 at week 12 (52.4% improvement; $p < 0.0001$). Six of the 10 participants experienced at least a 50% improvement based on the EASI after 12 doses. Using a visual analog score, pruritus levels decreased from $6.9 \text{ cm} \pm 1.8 \text{ cm}$ to $4.9 \text{ cm} \pm 2.5 \text{ cm}$ ($p < 0.015$). The subjects tolerated the drug well. One of the 10 suffered a serious adverse event. This patient developed thrombocytopenia that occurred during therapy and persisted even after cessation of drug. All but one of the patients had gradual return of disease to baseline 4–8 weeks after cessation of the drug. They were transitioned to topical therapy and systemic agents. One subject experienced a worsening of disease beyond baseline levels (204% increase in EASI) after discontinuation of disease. Although it is difficult to apply these results to larger populations as a result of the small sample size and lack of a control group, the authors concluded that it demonstrates promise that efalizumab may serve as an alternative to current systemic immunosuppressants used for AD (11).

Alopecia areata

Alopecia areata is theorized to be an autoimmune disease in which T lymphocytes target hair follicles. Treatment of the disease, especially the totalis and universal subtypes, is difficult. Kaelin et al. (12) proposed that efalizumab may be a novel option as the drug inhibits T-cell activation and migration. They reported a case of a 19-year-old male with alopecia areata partim universalis who saw dramatic response from treatment with efalizumab. The patient, who also had a history of Hashimoto's thyroiditis, atopic eczema, and hemophilia A, had alopecia of the whole scalp and body except for eyebrows and eyelashes. Potent topical steroids were unsuccessful, and he refused systemic steroid therapy. He commenced efalizumab therapy with an initial dose of 0.7 mg/kg/week followed by 1 mg/kg/week thereafter. The first regrowth of hair began after 1 month, on the scalp. After 6 months of treatment, 90% regrowth was achieved on the scalp, and 30–40% regrowth in the pubic

and axillary region. Interestingly, the patient had concomitant marked improvement of his atopic eczema. This case suggests that further studies are needed to evaluate the long-term efficacy and safety of efalizumab in alopecia areata (12).

Oral erosive lichen planus

Efalizumab may be useful in the treatment of oral lichen planus. Cell-mediated immunity is thought to play a role in the disease. Cheng and Mann (13) presented a case of a 54-year-old woman with a 3-month history of progressive painful lesions on her tongue and oral mucosa. Her primary care physician treated her with nystatin and hydrogen peroxide, and then acyclovir ointment. She then developed pruritic violaceous/erythematous papules on her body in addition to the oral lesions. She was started on a course of prednisone as well as topical tacrolimus therapy, which did result in modest improvement; however, the painful oral lesions persisted. Three weeks after cessation of steroids, efalizumab therapy was initiated with a dose of 0.7 mg/kg/week followed by 1 mg/kg/week thereafter. After 10 weeks, the patient experienced significant improvement in both oral (approximately 75%) and cutaneous lesions (13).

Recently Heffernan et al. (14) evaluated the efficacy of efalizumab in the treatment of oral erosive lichen planus, in a single-center, open-label, prospective pilot study. The primary efficacy outcome measure was the change in oral mucosal surface area involvement after 12 weeks of treatment. Secondary outcome measures included the 100-mm visual analog scale (VAS) for pain and a modified oral health impact profile (OHIP-14) questionnaire. Four adult patients with oral erosive lichen planus were enrolled and treated with efalizumab 0.7 mg/kg subcutaneously at week 0 followed by 1 mg/kg weekly from week 1 to week 11. The authors found that the mean reduction in the affected mucosal surface area was 71.1% (range 57.3% to 96.8%). The mean improvement in the 100-mm VAS for pain was 82%. The mean improvement in the OHIP-14 questionnaire was 69.3% (14).

Cutaneous lupus erythematosus

There are patients with subacute cutaneous lupus erythematosus (SCLE) that fail to respond to conventional therapies, including sunscreens, topical and oral steroids, dapsone, antimalarials, and cyclosporine. Clayton et al. (15) reported the case of a patient who responded dramatically to efalizumab. This 47-year-old woman developed

annular eruptions on the face trunk and limbs diagnosed as SCLE. She was treated with numerous agents (16 in total) all of which were discontinued secondary to poor response or adverse effects. Efalizumab was started at a dose of 1 mg/kg/week, and her cutaneous lesions began to improve dramatically within 6 weeks. During therapy, she experienced a flare that was controlled by increasing the dose to 1.25 mg/kg/week. At the time the report was written, the patient had been on the drug for 5 months without any adverse effects. The authors propose that efalizumab may represent an alternative treatment for SCLE when standard treatments fail (15).

Efalizumab has also been used in the treatment of discoid lupus erythematosus (DLE) (16). Because DLE is known to be predominantly T-cell mediated, the authors utilized efalizumab as a T-cell modulator in patients with recalcitrant disease. Thirteen patients received efalizumab, with treatment responses varying from good to excellent in 12 of 13 patients. There was a significant reduction in the cutaneous lupus activity and severity score after therapy with efalizumab ($P = .002$). The mean time to response being was 5.5 weeks (16).

Disseminated granuloma annulare

The pathogenesis of granuloma annulare remains unclear. The presence of infiltrating activated T lymphocytes on biopsy suggests that the entity may represent a T cell mediated process. Goffe (17) reported the case of a patient with psoriasis and disseminated granuloma annulare (DGA) who entered an efalizumab phase 3 clinical trial for patients with moderate to severe chronic plaque psoriasis. He received efalizumab for 12 weeks, followed by a longer course of weekly open-label treatment. Within 4 weeks of initiation of therapy, the DGA began clearing with complete resolution by the end of the trial. With continued weekly doses, the improvement was maintained. This experience has not been replicated in any other reports.

Conclusion

Efalizumab has been approved for the treatment of adult patients with chronic moderate to severe plaque psoriasis. The drug has demonstrated safety, efficacy, and quality-of-life improvements in trials, as well as in clinical practice. In addition, in an open-label study, efalizumab showed a sustained efficacy and safety profile with continuous long-term therapy, for up to 3 years (8). Clinical studies

and anecdotal reports have indicated success in hand and foot psoriasis, overweight patients, and those with inadequate response to TNF-inhibitors. In addition, case reports suggest other potential uses within the field of dermatology, including atopic dermatitis and oral erosive lichen planus.

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