Long-term continuous efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: Updated results from an ongoing trial

Alice B. Gottlieb, MD, PhD,[a] Tiffani Hamilton, MD,[b] Ivor Caro, MD,[c] Paul Kwon, MD,[c] Peter G. Compton, MA,[c] and Craig L. Leonardi, MD,[d] for the Efalizumab Study Group
New Brunswick, New Jersey; Atlanta, Georgia; South San Francisco, California; and St. Louis, Missouri

Background: Efalizumab is a T cell–targeted therapy for psoriasis.

Objective: We sought to evaluate the efficacy and safety of long-term, continuous efalizumab therapy.

Methods: Of 339 patients enrolled in this ongoing, open-label, phase III study, after 3 months 290 qualified for and entered the maintenance treatment phase.

Results: Results for the first 27 months of this 36-month continuous therapy trial are available. At month 3, 41% of patients achieved at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score; at month 27, 47% achieved at least a 75% reduction in PASI score (intent to treat, n = 339). Among patients eligible for maintenance therapy (n = 290), 56% achieved at least a 75% reduction in PASI score at month 27. Moreover, the at least 90% reduction in PASI score rate increased through 18 months (33%). The safety profile with efalizumab was sustained throughout 27 months of continuous treatment with no new common events over time.

Limitations: Because the extended treatment period was not a randomized clinical trial, no formal comparative analyses versus placebo were conducted. Three-month placebo data from randomized, parallel, placebo-controlled studies are briefly discussed.

Conclusions: These results suggest that efalizumab maintains, and in some patients continues to improve, efficacy during long-term therapy. (J Am Acad Dermatol 2006;54:S154-63.)

Patients with plaque psoriasis are often given a diagnosis before 30 years of age[1] and, thus, typically require decades of treatment to control their symptoms. Although traditional systemic therapies provide adequate disease control in many patients, they are associated with significant cumulative toxicities that generally preclude long-term treatment. Examples of safety concerns include hepatotoxicity with methotrexate, nephrotoxicity with cyclosporine, increased risk of skin cancer with phototherapy and cyclosporine, and teratogenicity with systemic retinoids.[2] To minimize the risk of end-organ damage, it is recommended that renal and hepatic function be monitored carefully during treatment with cyclosporine and methotrexate, respectively. Consensus conference guidelines recommend that physicians limit cyclosporine treatment to intermittent 3-month treatment cycles or, for some patients, extended treatment of a maximum of 2 years duration; however, the prescribing

From the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School[a]; Atlanta Dermatology, Vein and Research Center LLC[b]; Genentech Inc, South San Francisco[c]; and St. Louis University School of Medicine.[d]

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Reprint requests: Alice B. Gottlieb, MD, PhD, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Clinical Research Center, 51 French St, New Brunswick, NJ 08901-0019. E-mail: alice.gottlieb@umdnj.edu.

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Abbreviations used:

ITT:	intent to treat
LOCF:	last observation carried forward
PASI:	Psoriasis Area and Severity Index
PASI-50:	at least 50% reduction in PASI score
PASI-75:	at least 75% reduction in PASI score
PASI-90:	at least 90% reduction in PASI score

information recommends a maximum of 1 year of continuous exposure.[3,4] For methotrexate, guidelines recommend liver biopsies for patients exceeding a cumulative dose of 1.5 g.[5]

In an attempt to minimize cumulative toxicities, physicians have adopted various strategies including rotational, sequential, combination, or intermittent treatment regimens.[6-8] The ongoing management of such regimens can be inconvenient and may generate an ongoing cycle of disease control and relapses. Given the chronicity of this disease and the early age at which many patients are given a diagnosis, there is a clear unmet need for psoriasis therapies that can be safely administered on a continuous long-term basis. Improved understanding of the role of the immune system in the pathogenesis of psoriasis has resulted in the development and approval of several biologic therapies specifically designed to modulate key pathogenic targets. Given their targeted mechanisms of action, it is hoped that biologic therapies will provide improved safety profiles relative to traditional systemic therapies.

Efalizumab is a recombinant, humanized, monoclonal immunoglobulin G-1 antibody that inhibits multiple T cell–mediated events known to be involved in the pathogenesis and maintenance of psoriatic plaques, including T-cell activation, T-cell trafficking to sites of cutaneous inflammation, and T-cell reactivation in the skin. Multiple phase III clinical trials have demonstrated the efficacy, safety, and health-related quality-of-life benefits of 3 and 6 months of efalizumab treatment in patients with moderate to severe chronic plaque psoriasis.[9-13] When efalizumab therapy was extended from 3 to 6 months, there was no increase in the overall incidence of adverse events nor was there evidence of cumulative toxicity or end-organ damage.

An open-label, phase III clinical trial has evaluated the safety, tolerability, and efficacy of up to 3 years of continuous efalizumab therapy. Preliminary analyses demonstrated the sustained efficacy and safety of up to 15 months of continuous efalizumab treatment.[14] Updated results for patients receiving continuous efalizumab therapy for the first 27 months of this trial are presented here.

METHODS

Study design

This ongoing, open-label, multicenter, phase III clinical trial is evaluating the safety, tolerability, and efficacy of up to 3 years of continuous efalizumab therapy in adults (aged ≥18 years) with moderate to severe chronic plaque psoriasis (Psoriasis Area and Severity Index [PASI] ≥12.0 at screening, and ≥10% of body surface area affected) who are candidates for systemic therapy. All sites received institutional review board approval before initiating the study and all patients provided signed informed consent.

Details concerning the study design were previously reported[14] and are summarized in Fig 1. During the first 12 weeks of the study, patients received a single conditioning dose (0.7 mg/kg) followed by 11 weekly doses of subcutaneous efalizumab (2 mg/kg). During weeks 9 through 12, patients were randomly assigned to receive concomitant fluocinolone acetonide ointment 0.025% (Synalar; Medicis, Scottsdale, Ariz) or placebo equivalent (white petrolatum ointment). Patients who achieved at least 50% improvement in PASI score (PASI-50) at week 12 relative to baseline or a static Physician's Global Assessment rating of "mild," "minimal," or "clear" were eligible to receive subcutaneous efalizumab (1 mg/kg/wk) as maintenance therapy. During months 4 to 15, if patients experienced a protocol-defined relapse (loss of ≥PASI-50 achieved between baseline and week 12), they immediately ended participation in their current 3-month segment and started their next segment at an escalated dosage of 2 mg/kg/wk. In patients with relapse, investigators had the option to temporarily increase the efalizumab dose to 3 or 4 mg/kg/wk within 4 weeks of the date of relapse only. After month 15, dose escalation was not permitted.

At the time that this study protocol was developed, efalizumab studies were ongoing to evaluate various dosages. Thus, the optimal dose of efalizumab was not known. When trials evaluating 1- and 2-mg/kg/wk dose levels were completed, the results showed no apparent difference in efficacy and safety between the two doses. The recommended dose of efalizumab is 1 mg/kg/wk.

During maintenance treatment, emollients (including Eucerin cream and white petrolatum), scalp preparations, topical psoriasis therapies (eg, corticosteroid preparations, including fluocinolone acetonide ointment 0.025%, coal tar preparations, anthralin, calcipotriene, and topical retinoids), or ultraviolet B phototherapy were allowed. Patients could self-administer efalizumab during the maintenance phase of the study.