

ORIGINAL ARTICLE

A Novel Targeted T-Cell Modulator, Efalizumab, for Plaque Psoriasis

Mark Lebwohl, M.D., Stephen K. Tyring, M.D., Ph.D., Tiffani K. Hamilton, M.D., Darryl Toth, M.D., Scott Glazer, M.D., Naji H. Tawfik, M.D., Ph.D., Patricia Walicke, M.D., Ph.D., Wolfgang Dummer, M.D., Xiaolin Wang, Sc.D., Marvin R. Garovoy, M.D., and David Pariser, M.D., for the Efalizumab Study Group

ABSTRACT

BACKGROUND

From the Mt. Sinai School of Medicine, New York (M.L.); the University of Texas Medical Branch, Galveston (S.K.T.); the Atlanta Dermatology, Vein, and Research Center, Alpharetta, Ga. (T.K.H.); Probitry Medical Research, Windsor, Ont., Canada (D.T.); Buffalo Grove, Ill. (S.G.); the Welborn Clinic, Evansville, Ind. (N.H.T.); Genentech, South San Francisco, Calif. (P.W., W.D., X.W.); Xoma, Berkeley, Calif. (M.R.G.); and the Eastern Virginia Medical School and Virginia Clinical Research, Norfolk, Va. (D.P.). Address reprint requests to Dr. Lebwohl at the Mt. Sinai School of Medicine, 5 E. 98th St., 12th Fl., Box 1048, New York, NY 10029-6574.

Interactions between leukocyte-function–associated antigen type 1 (LFA-1) and intercellular adhesion molecules are important in the pathogenesis of psoriasis. Efalizumab, a humanized monoclonal antibody, binds to the α subunit (CD11a) of LFA-1 and inhibits the activation of T cells.

METHODS

In a phase 3, multicenter, randomized, placebo-controlled, double-blind study, we assign 597 subjects with psoriasis to receive subcutaneous efalizumab (1 or 2 mg per kilogram of body weight per week) or placebo for 12 weeks. Depending on the response after 12 weeks, subjects received an additional 12 weeks of treatment with efalizumab or placebo. Study treatments were discontinued at week 24, and subjects were followed for an additional 12 weeks.

RESULTS

At week 12, there was an improvement of 75 percent or more in the psoriasis area-and-severity index in 22 percent of the subjects who had received 1 mg of efalizumab per kilogram per week and 28 percent of those who had received 2 mg of efalizumab per kilogram per week, as compared with 5 percent of the subjects in the placebo group ($P < 0.001$ for both comparisons). Efalizumab-treated subjects had greater improvement than those in the placebo group as early as week 4 ($P < 0.001$). Among the efalizumab-treated subjects who had an improvement of 75 percent or more at week 12, improvement was maintained through week 24 in 77 percent of those who continued to receive efalizumab, as compared with 20 percent of those who were switched to placebo ($P < 0.001$ for both comparisons). After the discontinuation of efalizumab at week 24, an improvement of 50 percent or more in the psoriasis area-and-severity index was maintained in approximately 30 percent of subjects during the 12 weeks of follow-up. Efalizumab was well tolerated, and adverse events were generally mild to moderate.

CONCLUSIONS

Efalizumab therapy resulted in significant improvements in plaque psoriasis in subjects with moderate-to-severe disease. Extending treatment from 12 to 24 weeks resulted in both maintenance and improvement of responses.

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CHRONIC PLAQUE PSORIASIS AFFECTS approximately 2 percent of the world's population and results in disability similar to or exceeding that associated with other major illnesses, such as diabetes mellitus, arthritis, depression, and cancer.^{1,2} Systemic therapies are limited by toxic effects (e.g., end-organ damage, bone marrow suppression, cancer, and teratogenesis), interactions with other drugs, and the need for extensive laboratory monitoring.³⁻⁷ The unmet need for safe and effective therapies, coupled with an improved understanding of the pathogenesis of psoriasis, has prompted the development of targeted biologic therapies.

Psoriasis is an incurable autoimmune disease that is mediated by T lymphocytes.⁸ A T-lymphocyte adhesion molecule, leukocyte-function-associated antigen type 1 (LFA-1), binds with intercellular adhesion molecule 1 (ICAM-1), facilitating processes relevant to the pathogenesis of psoriasis, including the migration of T lymphocytes from the circulation into dermal and epidermal tissues, with subsequent reactivation.⁹ Monoclonal antibodies against LFA-1 inhibit the activation of T lymphocytes and their adhesion to the vascular endothelium, providing the basis for the targeting of LFA-1 for psoriasis.¹⁰⁻¹³ Efalizumab, a humanized monoclonal IgG₁ antibody, binds to the α subunit of LFA-1 (CD11a), inhibiting the binding of T lymphocytes to endothelial cells, their movement from the circulation into dermal and epidermal tissues, and their activation and reactivation. This activity differentiates efalizumab from the biologic agent that has been approved for psoriasis, alefacept, in that efalizumab inhibits T-lymphocyte activation without depleting memory effector T lymphocytes.¹⁴

Efalizumab's biologic effects and clinical activity were demonstrated in phase 1 and 2 studies.¹⁵⁻¹⁸ Efalizumab saturated CD11a on peripheral T lymphocytes and decreased epidermal thickness, the numbers of epidermal and dermal T lymphocytes, and the expression of keratin 16 and ICAM-1. These changes were accompanied by significant clinical improvement. We conducted a phase 3 trial to evaluate the efficacy and safety of efalizumab in subjects with moderate-to-severe plaque psoriasis.

METHODS

CONDUCT OF THE STUDY

Employees of Genentech and academic investigators, including the authors of this article, collabo-

rated in the design of the study. All the investigators were responsible for gathering the data, and Genentech employees held and analyzed the data. All authors had full access to the data and participated in their interpretation. Dr. Lebowhl made the decisions about publication.

STUDY SUBJECTS

The criteria for eligibility were an age of 18 to 70 years, plaque psoriasis that had been clinically stable for at least three months and that had been moderate to severe for at least six months, a psoriasis area-and-severity index of at least 12.0 at screening, the presence of plaque psoriasis covering at least 10 percent of the body-surface area, and candidacy for systemic therapy. The criteria for exclusion included a history of or ongoing uncontrolled infection, the presence of cancer or a history of cancer within the previous five years (excluding resolved basal-cell or squamous-cell skin cancers), hepatic or renal dysfunction, a white-cell count of less than 4000 per cubic millimeter or more than 14,000 per cubic millimeter, a history of severe allergic or anaphylactic reaction to humanized monoclonal antibodies, and previous treatment with efalizumab. After enrollment, the following factors resulted in withdrawal from the study: pregnancy, treatment with a live-virus or live-bacteria vaccine, the use of systemic or topical therapies for psoriasis (including phototherapy) that were not permitted in the study, the use of immunosuppressive agents, the use of experimental treatments, and any medical condition that could jeopardize the subject's safety. All subjects provided written informed consent. The institutional review board at each site approved the study protocol.

STUDY DESIGN

This phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial (conducted from May 4, 2000, through June 6, 2001) involved three consecutive phases: the first-treatment phase (weeks 0 through 12), the extended-treatment phase (weeks 13 through 24), and the follow-up phase (weeks 25 through 36) (Fig. 1). In the first phase, subjects were randomly assigned in a ratio of 2:2:1 to 1 mg of subcutaneous efalizumab (anti-CD11a, Raptiva, Genentech) per kilogram of body weight per week, 2 mg of efalizumab per kilogram per week, or an equivalent volume of matching placebo. To maintain blinding, two different volumes of placebo were used to match the two doses

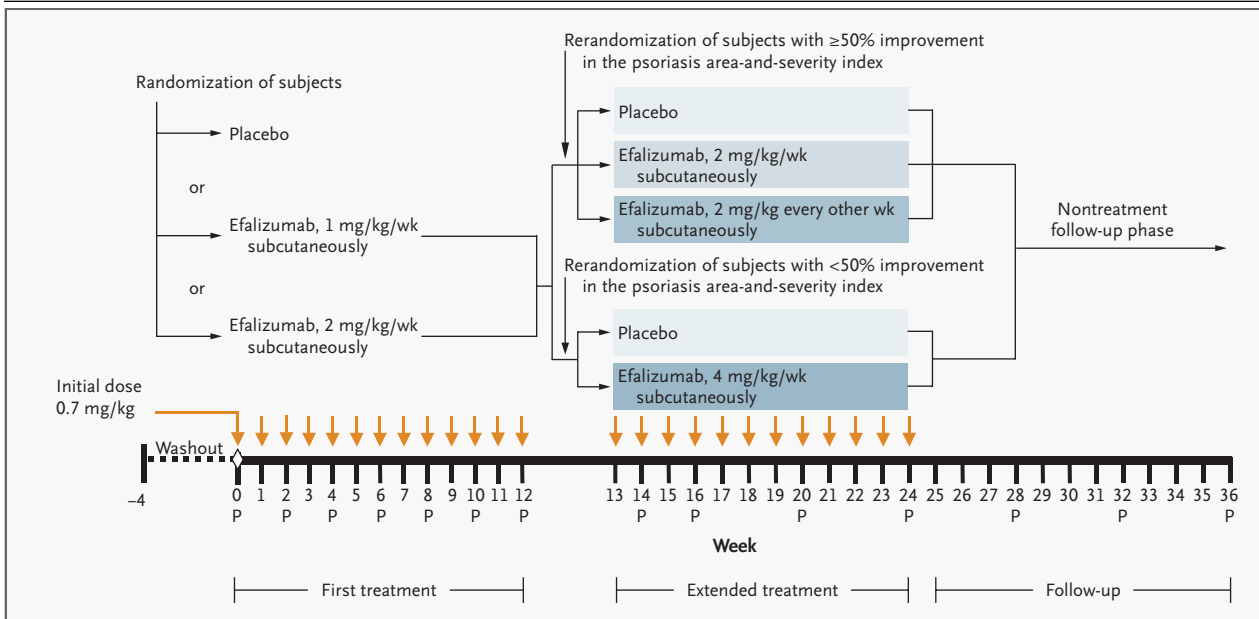


Figure 1. Study Design.

Before study treatment began, there was a 28-day washout phase, during which systemic therapy (including immunosuppressive therapy) and psoralen–ultraviolet A phototherapy were not administered; ultraviolet B phototherapy and topical treatments were discontinued 14 days before the beginning of study treatment. For the first-treatment phase (weeks 0 through 12), the initial dose was a conditioning dose of 0.7 mg per kilogram of body weight in order to minimize the first-dose effects; this was followed by 11 weekly subcutaneous doses of study drug, beginning 1 week after the conditioning dose. For the extended-treatment phase (weeks 13 through 24), subjects who had an improvement of at least 50 percent in the psoriasis area-and-severity index at 12 weeks underwent rerandomization (in a ratio of 1:1:1) and received a second conditioning dose of 0.7 mg per kilogram, followed by either placebo or doses of 2.0 mg of efalizumab per kilogram either weekly or every other week, beginning 1 week after the conditioning dose. Subjects who did not have an improvement of at least 50 percent in the psoriasis area-and-severity index at 12 weeks underwent rerandomization (in a ratio of 2:1) to receive two conditioning doses (0.7 mg per kilogram on day 0 of extended treatment and 2.0 mg per kilogram on day 7 of extended treatment) followed by 4.0 mg of efalizumab per kilogram or placebo weekly, beginning 1 week after the second conditioning dose. All subjects included in this report received efalizumab during weeks 0 through 12; therefore, placebo treatment during the extended-treatment phase represents withdrawal from efalizumab. The administration of the study drug ceased at week 24; subjects immediately entered a follow-up phase (weeks 25 through 36) during which the same requirements regarding concomitant medications that were in place during weeks 0 through 24 continued to apply. P denotes an assessment of the psoriasis area-and-severity index.

of active drug. Randomization was performed according to a dynamic approach (urn adaptive biased-coin)¹⁹ and was balanced within subgroups defined according to the base-line psoriasis area-and-severity index (≤ 16 vs. > 16), receipt or nonreceipt of previous systemic treatment for psoriasis, and study site.

In the second phase, subjects who had been receiving active treatment were stratified into three subgroups on the basis of their level of improvement on the psoriasis area-and-severity index from base line to week 12 (≥ 75 percent, 50 to 74 percent, or < 50 percent). Subjects in the first two strata were randomly assigned to continue receiving 2 mg of efalizumab per kilogram either weekly or every other week or to receive placebo. Rerandomization for

efalizumab-treated subjects was balanced within subgroups defined according to the dose received during the first-treatment phase, with the use of static randomization tables with a block size of six. Subjects in the third stratum (< 50 percent improvement) were randomly assigned to either an increased dose of efalizumab (4 mg per kilogram per week) or placebo. In the follow-up phase, the treatments were discontinued, and subjects were followed for an additional 12 weeks.

The use of Eucerin cream (Beiersdorf), tar or salicylic acid preparations for psoriasis on the scalp, limited application of low-potency (group VII) corticosteroids, and oral antipruritic agents was permitted. Subjects could self-administer approximately half the injections during weeks 13 through 24 at

home. All other injections were administered in the clinic.

ASSESSMENT OF RESPONSES

Responses were assessed with the use of the psoriasis area-and-severity index, a measure used by the Food and Drug Administration (FDA) in clinical trials to assess the efficacy of therapies for psoriasis. The score, based on the extent of the skin-surface area involved and the severity of erythema, desquamation, and plaque induration, ranges from 0 to 72, with higher scores indicating more severe disease and a reduction in the score indicating improvement.²⁰

STATISTICAL ANALYSIS

The investigators, the sponsor, and the contract research organization remained unaware of the treatment-group assignments until all data analyses were completed. The population included in the primary analysis was the intention-to-treat population consisting of all the subjects who underwent randomization. Subjects were considered to have had a treatment failure if the value for the psoriasis area-and-severity index at week 12 was missing.

Fisher's exact test was used for the comparison of each efalizumab group with the placebo group in terms of the proportion of subjects who had an improvement of at least 75 percent in the psoriasis area-and-severity index, the primary end point. For all analyses of weeks 1 through 12, data for the two placebo groups were combined. To maintain a two-sided type I error of 0.05, the Hochberg-Bonferroni procedure for multiple comparisons was used. If both comparisons resulted in a difference in favor of efalizumab with a P value of less than 0.05, the data from both efalizumab groups were considered to be significantly different from those in the placebo group. If the P value for one comparison exceeded 0.05, the data from the other efalizumab group were considered to be significantly different from those in the placebo group if the difference in favor of efalizumab was associated with a P value of less than 0.025.

The planned accrual was 500 subjects (400 randomly assigned to efalizumab and 100 to placebo). The probability that there would be at least one type of adverse event with an actual rate of 1 percent in a group of 200 subjects was 0.866, and the probability that there would be at least one type with an actual rate of 2 percent was 0.982. The estimation of the statistical power was based on the assumption

of a response rate of 25 percent in the efalizumab groups and 2 percent in the placebo group. The study had more than 95 percent power to detect the difference in the rate of the primary end point at the 0.025 level with the use of Fisher's exact test. For secondary analyses, two-sample t-tests using the pooled error term from an analysis of variance including all treatment groups were used for continuous variables, and Fisher's exact test was used for dichotomous variables.

RESULTS

CHARACTERISTICS OF THE SUBJECTS

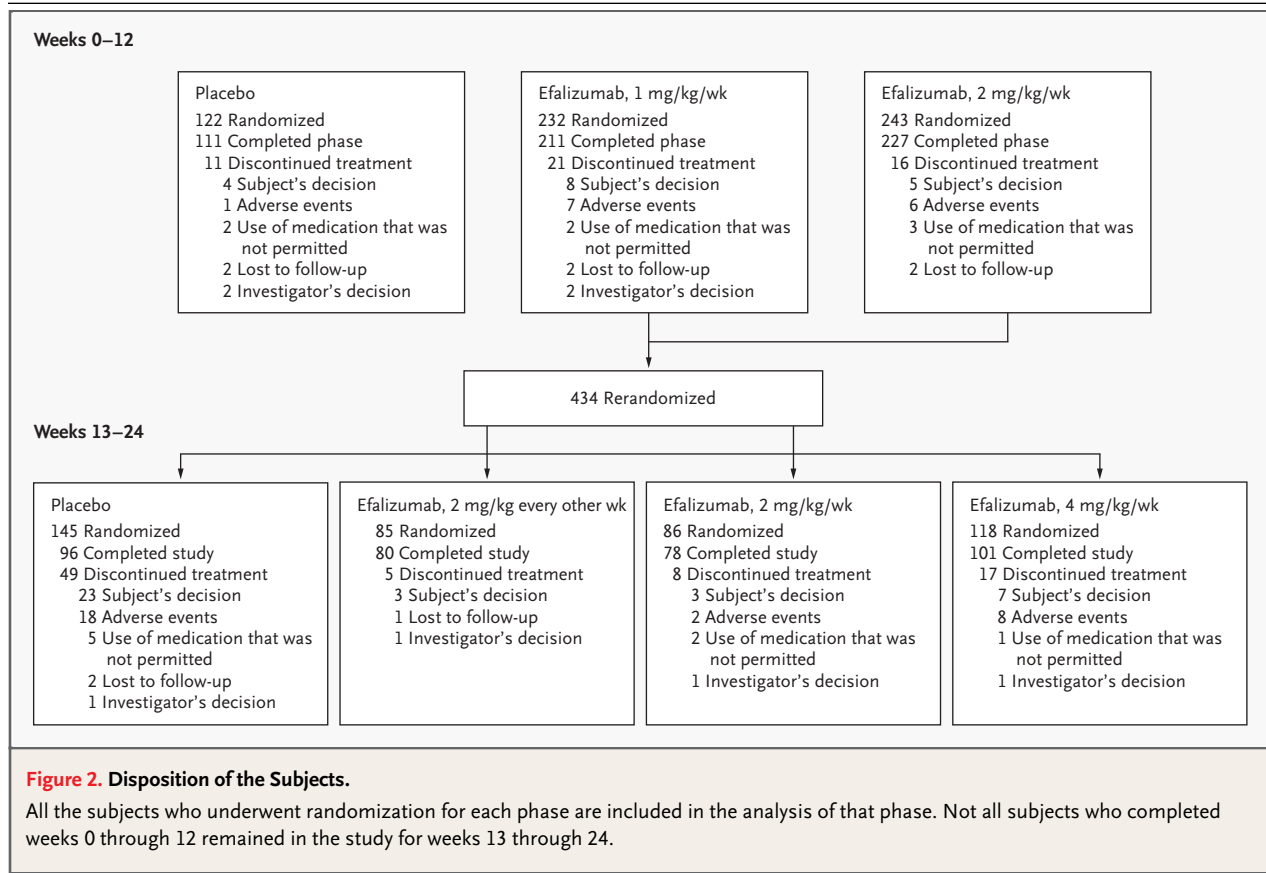
A total of 597 subjects underwent randomization (Fig. 2), and there were no significant differences among the treatment groups with respect to demographic characteristics, other base-line characteristics, or the severity of disease. Overall, 65 percent of the subjects were male, the mean age was 46 years, the mean duration of psoriasis was 19 years, the mean base-line psoriasis area-and-severity index was 20.0, and 67 percent of the subjects had received previous systemic therapy for psoriasis. Seventy-seven percent of the subjects received all 12 doses of study drug during the first-treatment phase, with a relatively even distribution among the groups.

A total of 434 subjects underwent rerandomization for the extended-treatment phase (Fig. 2). The groups for this phase were similar in terms of base-line characteristics. Seventy percent of the subjects who were assigned to receive efalizumab weekly during the extended-treatment phase and 87 percent of the subjects assigned to receive efalizumab every other week received all scheduled doses, either at home or in the clinic.

TREATMENT EFFICACY

First-Treatment Phase

The subjects in both efalizumab groups had a significantly better response than those in the placebo group, as determined by the assessment of the primary end point and all other prespecified measures ($P < 0.001$ for the comparisons with the placebo group in the proportion of subjects with an improvement of at least 50 percent and the proportion with an improvement of at least 75 percent) (Table 1). Responses in various subgroups defined according to site, sex, age group, base-line psoriasis area-and-severity index, or receipt or nonreceipt of previous systemic therapy were generally consistent with those in the overall study population. Efalizumab



therapy resulted in a significantly lower mean psoriasis area-and-severity index at week 12 than that found in the placebo group (9 vs. 17, $P < 0.001$ according to a post hoc analysis); there was a mean improvement of 51 percent in the 1-mg-efalizumab group and 52 percent in the 2-mg-efalizumab group, as compared with 17 percent in the placebo group ($P < 0.001$ for both comparisons). Improvement in the efalizumab groups significantly diverged from that in the placebo group at week 4 ($P < 0.001$ for both comparisons) (Fig. 3). Photographs illustrating improvement are shown in Figure 4.

Extended-Treatment Phase

Of the 121 efalizumab-treated subjects who had an improvement of at least 75 percent in the psoriasis area-and-severity index at week 12, 119 underwent rerandomization to the continuation of efalizumab treatment with 2 mg per kilogram either weekly or every other week or to the cessation of active treatment (the administration of placebo). An improvement of 75 percent or more in the psoriasis area-and-severity index was maintained in a signifi-

cantly greater proportion of the subjects who were treated with efalizumab during this phase than of those given placebo ($P < 0.001$ for the comparisons between each of the efalizumab groups and the placebo group). Therefore, continued therapy with efalizumab either weekly or every other week was beneficial (Table 1).

Of the subjects in the efalizumab groups who had an improvement of 50 to 74 percent in the psoriasis area-and-severity index at week 12, 138 underwent rerandomization to the continuation of efalizumab treatment with 2 mg per kilogram either weekly or every other week or to placebo. An improvement of 75 percent or more in the psoriasis area-and-severity index was achieved in a significantly greater proportion of the efalizumab-treated subjects than of those given placebo. Therefore, continued therapy with efalizumab either weekly or every other week was also beneficial in these subjects (Table 1).

Of the 182 subjects who received efalizumab and had an improvement of less than 50 percent in the psoriasis area-and-severity index at week 12,

177 underwent rerandomization to the continuation of efalizumab treatment with 4 mg per kilogram per week or to placebo. An improvement of 75 percent or more in the psoriasis area-and-severity index was achieved at week 24 in a significantly greater proportion of efalizumab-treated subjects than of those given placebo ($P=0.02$) (Table 1). Therefore, there is evidence to suggest that the escalation of the dose was beneficial in the subjects who had had a limited response to the initial dose.

Follow-up Phase

At week 36, 12 weeks after the discontinuation of the study treatment, 50 percent or more of the improvement that had been achieved during treatment was maintained in approximately one third of the subjects who had received continuous efalizumab therapy for 24 weeks. Among the remaining subjects, the mean psoriasis area-and-severity index gradually regressed toward the base-line value. The time to relapse (loss of at least 50 percent of the improvement in the psoriasis area-and-severity index that had been achieved between base line and week 24) among subjects who had had an improvement of at least 50 percent at week 24 was approximately 84 days.

SAFETY

In general, efalizumab therapy was well tolerated. The rates of adverse events that were reported in at least 5 percent of the subjects in any treatment group and that occurred at a rate at least 1 percentage point higher in an efalizumab group than in the placebo group are shown in Table 2. During weeks 0 through 12, 10 types of adverse events occurred at a rate at least 5 percentage points higher in an efalizumab group than in the placebo group. Of these events, headache, chills, fever, nausea, and myalgia were predefined as acute adverse events when they occurred on the day of or within two days after the administration of a dose of the study drug. Acute adverse events were most frequent after the first dose, were generally mild to moderate, and decreased in frequency over time. By the third dose and for subsequent doses, the percentage of subjects in each group who had acute adverse events was similar. Serious adverse events and adverse events leading to withdrawal from the study were infrequent, and their rates were similar in the efalizumab groups and the placebo group (Table 2).

During weeks 13 through 24, the rates of adverse events were similar to those observed during weeks

Table 1. Improvements in the Psoriasis Area-and-Severity Index at Week 12 among All Subjects and at Week 24 among Subjects Treated with Efalizumab during Weeks 0 through 12.*

Variable	Improvement in the Psoriasis Area-and-Severity Index		
	≥50 Percent no./total no. (%)	≥75 Percent	≥90 Percent
Week 12 response			
Placebo	19/122 (16)	6/122 (5)	1/122 (<1)
Efalizumab, 1 mg/kg/wk	120/232 (52)†	52/232 (22)†	10/232 (4)
Efalizumab, 2 mg/kg/wk	138/243 (57)†	69/243 (28)†	15/243 (6)
Week 24 response			
Subjects with improvement of ≥75% at wk 12			
Placebo	16/40 (40)	8/40 (20)	1/40 (2)
Efalizumab, 2 mg/kg every other wk	38/40 (95)	31/40 (78)†	13/40 (32)
Efalizumab, 2 mg/kg/wk	35/39 (90)	30/39 (77)†	12/39 (31)
Subjects with improvement of 50–74% at wk 12‡			
Placebo	5/46 (11)	2/46 (4)	0
Efalizumab, 2 mg/kg every other wk	30/45 (67)	13/45 (29)§	3/45 (7)
Efalizumab, 2 mg/kg/wk	35/47 (74)	25/47 (53)†	1/47 (2)
Subjects with improvement of <50% at wk 12			
Placebo	9/59 (15)	1/59 (2)	1/59 (2)
Efalizumab, 4 mg/kg/wk	47/118 (40)	15/118 (13)¶	5/118 (4)

* The psoriasis area-and-severity index, based on skin-surface involvement and the severity of erythema, desquamation, and plaque induration, ranges from 0 to 72, with higher scores indicating more severe disease and a reduction in the scores indicating improvement. The week 12 value for the index was missing for 11 subjects in the placebo group (9 percent), 19 subjects in the 1-mg-efalizumab group (8 percent), and 16 subjects in the 2-mg-efalizumab group (7 percent); therefore, these subjects were classified as having an improvement of less than 50 percent for the purposes of the analysis of the primary efficacy end point. These patients discontinued the study and did not undergo rerandomization.

† $P<0.001$ for the comparison with the placebo group.

‡ According to the case report forms, 137 subjects had an improvement of 50 to 74 percent at week 12; however, the randomization system randomly assigned a total of 138 subjects to extended treatment.

§ $P=0.002$ for the comparison with the placebo group.

¶ $P=0.02$ for the comparison with the placebo group.

0 through 12, with the exception of a lower rate of occurrence of acute adverse events. Adverse events resulting in early withdrawal from the study were more common among subjects receiving placebo than among those receiving efalizumab. The rate of infection among subjects who continued to receive efalizumab was similar to that observed during the first 12 weeks, after adjustment for the season during which the treatment was received.

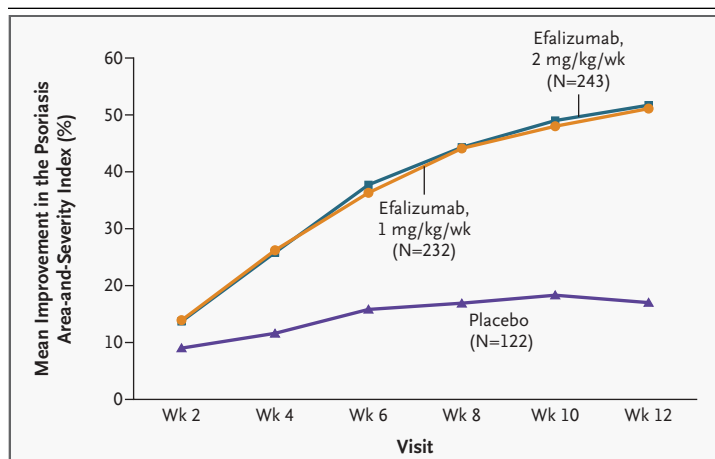


Figure 3. Mean Improvements in the Psoriasis Area-and-Severity Index during the First-Treatment Period.

The psoriasis area-and-severity index, based on skin-surface involvement and the severity of erythema, desquamation, and plaque induration, ranges from 0 to 72, with higher scores indicating more severe disease and a reduction in the scores indicating improvement.

During the follow-up phase, the types of adverse events that occurred in at least 5 percent of all subjects were nonspecific infection (in 13 percent), worsening psoriasis (9 percent), pruritus (6 percent), and arthritis (5 percent). Thirteen subjects (3 percent) had a serious adverse event (five of which were nonfatal infections and three of which were psoriasis-related events); none of these events resulted in withdrawal from the study.

Anti-efalizumab antibodies developed in 5 percent of the subjects who were treated with efalizumab. There was no difference between the safety profile among these subjects and that among the subjects who did not have anti-efalizumab antibodies. The absolute lymphocyte, eosinophil, and total white-cell counts were transiently elevated during efalizumab treatment; they returned to their base-line levels on the discontinuation of treatment. Alkaline phosphatase and serum glutamate pyruvate transaminase levels were slightly elevated transiently during efalizumab treatment, although these elevations were deemed not to be clinically relevant. There were no other notable changes in laboratory results or vital signs.

DISCUSSION

Efalizumab therapy resulted in significant improvement and was well tolerated in subjects with mod-

erate-to-severe plaque psoriasis. At week 12, significantly more subjects in the efalizumab groups than in the placebo group had an improvement of 75 percent or more in the psoriasis area-and-severity index. Improvement in the efalizumab group diverged significantly from that in the placebo group by week 4. A response to phototherapy, including psoralen-ultraviolet A therapy, generally occurs after eight weeks. With systemic therapy, a response to cyclosporine typically occurs at four weeks, a response to methotrexate at four to six weeks, and a response to retinoids and alefacept even later (at more than eight weeks). Thus, efalizumab has a rapid onset of action that compares favorably with those of current therapies.^{21,22}

Continued efalizumab therapy provided continued benefit. In most subjects in the efalizumab group who had an improvement of 75 percent or more in the psoriasis area-and-severity index at week 12, the response was maintained with continued treatment through week 24. In approximately 90 percent of these subjects, an improvement of at least 50 percent in the psoriasis area-and-severity index was maintained at week 24, illustrating the benefit of continued therapy. The high percentage of subjects in the placebo group who had an improvement of at least 50 percent during weeks 13 through 24 may reflect the fact that these subjects received efalizumab during weeks 0 through 12 and had residual clinical benefit. In addition, extending the efalizumab treatment from 12 to 24 weeks resulted in improved responses in many subjects who did not initially have improvement of 75 percent or more.

The gradual loss of clinical benefit observed after the discontinuation of efalizumab therapy may have been due in part to the fact that the study design dictated an abrupt discontinuation of efalizumab treatment, without tapering or a transition to other therapies for psoriasis, which is not consistent with general practice. The natural course of psoriasis is marked by fluctuations in severity over time,²³ and given that psoriasis is incurable, the disease eventually returns after the discontinuation of all psoriasis therapies. We speculate that psoriasis might be best controlled by the continuous administration of efalizumab.

The psoriasis area-and-severity index is widely used to evaluate efficacy during clinical trials. However, the responses to traditional psoriasis therapies vary among different groups of patients and according to the severity of the psoriasis being examined



Figure 4. Representative Responses to Efalizumab.

Panels A and B show the same subject at base line and at day 84 of efalizumab therapy, respectively; the change reflects an improvement of at least 75 percent in the psoriasis area-and-severity index. Panels C and D show a different subject at base line and at day 84 of efalizumab therapy; the change in this subject reflects an improvement of 50 to 74 percent in the psoriasis area-and-severity index.

and the type of monitoring that is performed (which, in turn, depends on whether the study is initiated by a drug manufacturer or independent investigators). Such variations make it difficult to compare emerging biologic therapies with FDA-approved agents in terms of the levels of improvement in the psoriasis area-and-severity index. This lack of comparability is highlighted by the recent trial compar-

ing methotrexate with cyclosporine for the treatment of plaque psoriasis.²⁴ For example, the baseline characteristics of the patients in that study were different from those in our study; on average, the patients were younger (41.6 years and 38.3 years vs. 46 years) and had a lower psoriasis area-and-severity index at base line (13.4 and 14.0 vs. 20.0). The time point at which the primary efficacy end point

Table 2. Adverse Events during the First-Treatment Phase.*

Type of Adverse Event	Placebo (N=122)	Efalizumab, 1 mg/kg/wk (N=232)	Efalizumab, 2 mg/kg/wk (N=243)	P Value†
	<i>number (percent)</i>			
Any‡	91 (75)	199 (86)	207 (85)	0.006
Headache	29 (24)	71 (31)	93 (38)	0.02
Infection	19 (16)	27 (12)	43 (18)	0.78
Nausea	11 (9)	34 (15)	35 (14)	0.14
Chills	3 (2)	38 (16)	31 (13)	<0.001
Pain	4 (3)	35 (15)	29 (12)	<0.001
Fever	6 (5)	26 (11)	29 (12)	0.03
Asthenia	7 (6)	17 (7)	27 (11)	0.28
Myalgia	5 (4)	16 (7)	22 (9)	0.17
Arthralgia	6 (5)	24 (10)	12 (5)	0.43
Pharyngitis	6 (5)	14 (6)	22 (9)	0.43
Rhinitis	8 (7)	18 (8)	13 (5)	1.00
Peripheral edema	5 (4)	14 (6)	12 (5)	0.65
Back pain	1 (1)	10 (4)	16 (7)	0.03
Herpes simplex	5 (4)	8 (3)	14 (6)	1.00
Cough increased	5 (4)	8 (3)	13 (5)	1.00
Vomiting	2 (2)	12 (5)	10 (4)	0.19
Worsening psoriasis	2 (2)	12 (5)	8 (3)	0.28
Acne	1 (1)	14 (6)	6 (2)	0.09
Serious adverse event	1 (1)	4 (2)	7 (3)	0.48
Adverse event leading to withdrawal from study	2 (2)	9 (4)	7 (3)	0.55

* Data are for the types of adverse events that occurred in at least 5 percent of the subjects in any treatment group and that occurred at a rate at least 1 percentage point higher in an efalizumab group than in the placebo group. Multiple occurrences of the same event in a single subject were counted once in the overall incidence.

† P values are for the comparisons between the combined efalizumab groups and the placebo group and were calculated with the use of post hoc, two-sided Fisher's exact tests, without adjustment for multiple comparisons.

‡ Data are the numbers and percentages of subjects with at least one adverse event.

was assessed differed, and the protocols differed in terms of whether or not active therapies for psoriasis were permitted during the follow-up period. Thus, despite a standardized efficacy end point,

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the comparison of efficacy between trials is complicated.

The adverse events that were attributed to efalizumab in our study were primarily mild to moderate. Except for acute adverse events — most commonly, headache, nausea, chills, and fever — the safety profile of efalizumab was similar during the 12-week treatment period and during the 24-week treatment period. Acute adverse events, observed primarily after the first or second dose, were managed easily and did not preclude further treatment. Acute adverse events are not uncommon after the administration of monoclonal antibodies or fusion proteins.^{25,26} The rate of infection was not increased with efalizumab, and there was no evidence of end-organ toxicity, which limits the use of some systemic therapies. Finally, the low incidence of the development of anti-efalizumab antibodies (5 percent) may make the long-term administration of efalizumab feasible.

Efalizumab compares favorably with approved antipsoriasis agents, demonstrating both rapid and sustained improvement. Although the long-term safety and efficacy of efalizumab in the treatment of psoriasis have not been established, the results of this trial show that the extension of efalizumab treatment resulted in the maintenance of and improvement in the responses in most subjects, thus demonstrating the benefit of continued treatment.

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