Efalizumab for Patients With Moderate to Severe Plaque Psoriasis

A Randomized Controlled Trial

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Context Because T-cell interactions are involved in the pathophysiology of psoriasis, therapy with a T-cell modulator may have beneficial effects on psoriasis severity and health-related quality of life (HRQL).

Objective To assess the efficacy and safety of efalizumab, a T-cell modulator, in patients with plaque psoriasis.

Design, Setting, and Patients Phase 3 randomized, double-blind, parallel-group, placebo-controlled trial involving 556 adult patients with stable, moderate to severe plaque psoriasis and conducted at 30 study centers in the United States and Canada between January and July 2002.

Interventions Patients were randomly assigned in a 2:1 ratio to receive 12 weekly doses of subcutaneous efalizumab, 1 mg/kg (n=369), or placebo equivalent (n=187).

Main Outcome Measures At least 75% improvement on the Psoriasis Area and Severity Index (PASI-75); improvement on the overall Dermatology Life Quality Index (DLQI), Itching Visual Analog Scale (VAS), and Psoriasis Symptom Assessment (PSA) at week 12 vs baseline.

Results Efalizumab-treated patients experienced significantly greater improvement on all end points than placebo-treated patients. Twenty-seven percent of efalizumab-treated patients achieved PASI-75 vs 4% of the placebo group ($P<.001$). Efalizumab-treated patients exhibited significantly greater mean percentage improvement than placebo-treated patients on the overall DLQI (47% vs 14%; $P<.001$), Itching VAS (38% vs –0.2%; $P<.001$), and PSA frequency and severity subscales (48% vs 18% and 47% vs 17%, respectively; $P<.001$ for both) at the first assessment point. Efalizumab was safe and well tolerated, with primarily mild to moderate adverse events.

Conclusion In this 12-week study, efalizumab resulted in significant improvements in clinical end points, including physician-assessed and dermatology-specific patient-reported HRQL measures, in patients with moderate to severe plaque psoriasis.

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PSORIASIS, A DISEASE AFFECTING millions of persons worldwide, is a chronic inflammatory disease that has a profound adverse effect on patients' physical, social, and mental well-being.[1-6] In the National Psoriasis Foundation survey of more than 17 000 respondents, 79% of patients with severe disease reported that psoriasis adversely affected their lives and limited activities of daily living (eg, work and school participation).[3]

The physical symptoms of psoriasis adversely affect daily functioning, with the most frequently reported symptoms including scaling, itching, and burning.[3,7,8] With inadequate control of these symptoms, physical, social, and mental functioning and overall health-related quality of life (HRQL) are compromised.[8,9] For example, the physical appearance of lesions can cause patients to experience stress and embarrassment[6,10] and have adverse effects on emotional aspects and normal functioning.[11] Up to 10% of psoriasis patients, especially younger patients, harbor suicidal thoughts compared with approximately 3% of general medical patients, indicating a significant unmet medical need.[3,12]

Efalizumab is a humanized monoclonal IgG1 antibody that targets T-cell interactions central to the patho-

See also p 3133 and Patient Page.

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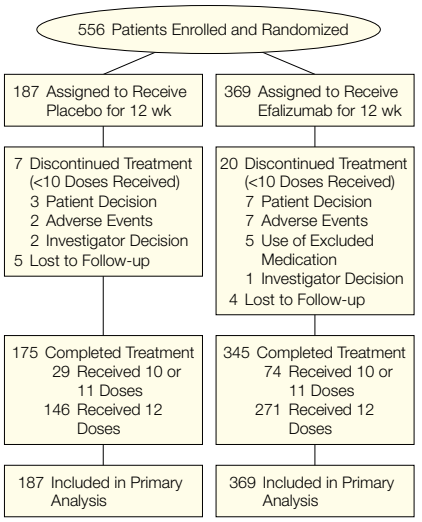
physiology of psoriasis.[13-23] In this study, the effect of efalizumab on dermatology-related HRQL in patients with moderate to severe plaque psoriasis was examined using a broad set of outcome measures including physicians' assessments and patients' perceptions.

Figure 1. Flow of Study Participants



METHODS

Protocol

This phase 3 randomized, double-blind, parallel-group, placebo-controlled multicenter trial evaluated the efficacy and safety of efalizumab (anti-CD11a; Raptiva, Genentech Inc) in adults with moderate to severe psoriasis. Eligible patients were 18 to 75 years of age, diagnosed as having plaque psoriasis for at least 6 months with at least 10% of total body surface area (BSA) affected, had a minimum Psoriasis Area and Severity Index (PASI) score of 12.0 at screening, and were candidates for systemic therapy. Patients could withdraw or be withdrawn from the study at any time. All sites received institutional review board approval prior to initiating the study, and all patients provided written informed consent.

Patients were randomly assigned to receive 12 weekly doses of either subcutaneous efalizumab, 1 mg/kg, or placebo equivalent, as per the original study protocol (FIGURE 1). Allocation sequences were generated by an unblinded statistician at Genentech Inc, the study sponsor, who then passed them to the interactive voice response system vendor. The sites enrolled and randomized patients by calling the interactive voice response system, which assigned patients to either efalizumab or placebo using a random permuted-block design to obtain approximately a 2:1 ratio within categories defined by the stratification variables: baseline PASI score (≤16.0 vs ≥16.1), prior treatment for psoriasis (yes vs no), and study center.

Each patient received an initial conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 1 mg/kg of study drug (efalizumab or placebo equivalent). After 12 weeks of placebo-controlled treatment, all patients were enrolled in a separate long-term open-label extension study.

Patients received efalizumab monotherapy, with all phototherapy and systemic therapy excluded. Patients were permitted to use emollients. Tar and salicylic acid preparations were permitted for the scalp, and low-potency topical corticosteroids were allowed for the face, hands, feet, groin, and axillae. Patients, investigators, sponsor, and the contract research organization were blinded regarding treatment assignment or active study drug until the analyses of all data were complete.

Assessments

The primary efficacy outcome measure was the proportion of patients with at least 75% improvement in PASI (PASI-75) at week 12 relative to baseline (BOX). The PASI is a physician-assessed score, recognized by the US Food and Drug Administration[24] to assess efficacy of psoriasis therapies in clinical trials, that takes into account the extent of involved skin surface area and severity of erythema, desquama-

Box. Efficacy Outcomes Assessed During the Study

Physician-Assessed Outcomes

Psoriasis Area and Severity Index (PASI): Assesses the extent of psoriasis on 4 body surface areas (head, trunk, and upper and lower limbs) and the degree of plaque erythema, scaling, and thickness. The PASI scores account for both the extent of body surface area affected by the erythema, scaling, and thickness and the severity of these measures. The score ranges from 0 (no disease) to 72 (maximal disease).

Overall Lesion Severity Scale (OLS): Static global assessment with 6 categories (clear, minimal, mild, moderate, severe, and very severe) based on the characteristics of plaque elevation, scaling, and erythema.

Physician's Global Assessment (PGA): Captures and categorizes the global response to therapy of all clinical signs and symptoms of disease relative to baseline. Physicians use all available information for the assessment, including subjective information gathered from the patient and photographs taken at baseline. The categories are worse, unchanged, slight, fair, good, excellent, and cleared.

Patient-Reported Outcomes

Dermatology Life Quality Index (DLQI): The DLQI is a 10-item questionnaire that incorporates patients' assessments of itch, pain, feelings of embarrassment and self-consciousness, problems with their psoriasis treatment, and interference of their psoriasis with daily activities, relationships, and sexual activity. The DLQI scores range from 0 (no impairment) to 30 (maximal impairment).

Itching Visual Analog Scale (VAS): The 10-point Itching VAS is a modified VAS with scores ranging from 0 (no itching) to 10 (severe itching).

Psoriasis Symptom Assessment (PSA): The PSA is a 16-item measure of 8 psoriasis-related cutaneous symptoms (hurt, burning or stinging, itched, bothered by water, irritated, sensitive, skin condition bled, scaling). The PSA contains 2 subscales, one measuring the frequency of the 8 symptoms and the other assessing how troublesome or bothersome psoriasis symptoms are.

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tion, and plaque induration.[25] The composite score ranges from 0 to 72, with higher numbers indicating more severe disease and a reduction in score representing improvement. The PASI components of lesion thickness, erythema, and scaling were examined separately. The PASI-75 is the currently recognized benchmark of end points used in psoriasis clinical trials.[26] For each study site, PASI assessments were performed by a single investigator who was blinded to randomization.

Secondary efficacy measures included 2 global physician assessments: a static measure designated the Overall Lesion Severity Scale (OLS) and a dynamic measure designated the Physician's Global Assessment (PGA). Additional secondary outcome measures were the proportion of patients with at least 50% improvement on the PASI (PASI-50) relative to baseline, the percentage of PASI improvement over time, PASI thickness component, and the percentage of BSA affected by psoriasis.

Patient-reported outcomes were evaluated using prospectively defined mean improvement in the overall Dermatology Life Quality Index (DLQI), Itching Visual Analog Scale (VAS), and Psoriasis Symptom Assessment (PSA) frequency and severity subscales. The overall improvement for all patient-reported outcomes was assessed at week 12 relative to baseline.

The DLQI measures the impact of skin disorders and treatment on patient functioning and well-being using a 7-day recall period.[27] The psychometric characteristics relating to the validity and reliability of the DLQI are well established.[27,28] The Itching VAS used in previous trials of efalizumab has been shown to be a valid and reliable measure.[28] The PSA is an adaptation of a validated skin disorder instrument, the Skindex,[29,30] with 2 additional questions related to the frequency and severity of skin scaling using a 2-week recall period. The PSA, also used in prior efalizumab studies, has been established to be a valid, reliable, and responsive measure.[28]

Baseline measurements were those made closest but prior to administration of the first dose of study drug. The PASI was assessed at baseline and every 2 weeks thereafter. The patient-reported outcomes (DLQI, Itching VAS, and PSA) were performed prior to obtaining physician assessments for measures (eg, PASI) at baseline and at weeks 4, 8, and 12.

The safety and tolerability of efalizumab were monitored by adverse events, vital signs, physical examination, clinical laboratory evaluation, and serum human antihuman antibody measurement. Adverse events were assessed weekly. Standard methods to assess safety were used.

Statistical Analyses

The sample size was based primarily on safety considerations. With a planned sample size of 333 patients in the efalizumab group and 167 patients in the placebo group, using a 2-sided Fisher exact test, the study had 99% power to detect a difference between the assumed placebo response rate of 5% and the assumed efalizumab response rate of 25% at an $\alpha = .05$ significance level. Analyses were conducted with nQuery Advisor software, version 4.0 (Statistical Solutions, Saugus, Mass).

The main analysis population for primary and secondary end points was the intention-to-treat population, consisting of all patients who were randomized whether or not they received any study drug or completed the full course of treatment. Patients were analyzed according to their randomized treatment group. Safety analyses were performed on an as-treated population.

The primary end point was evaluated by comparing the proportion of those in the efalizumab group and those in the placebo group who achieved PASI-75 at week 12 relative to baseline using a 2-sided Fisher exact test for binomial outcome at the .05 level of significance; the exact 95% confidence interval for response rates within each treatment group and the difference in response rates between the efalizumab and placebo group were calculated. Patients who discontinued early from the study or whose week 12 PASI score was missing were classified as nonresponders.

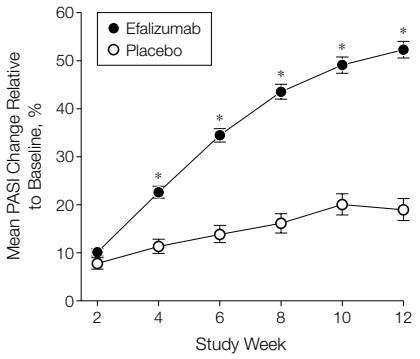
The following secondary end points were compared between treatment groups using a 2-sided Fisher exact test

Table 1. Baseline Characteristics of Study Participants*

Characteristics	Placebo (n = 187)	Efalizumab (n = 369)
Sex, No. (%)		
Male	132 (71)	251 (68)
Female	55 (29)	118 (32)
Race/ethnicity, No. (%)		
White	167 (89)	331 (90)
Hispanic	7 (4)	17 (5)
Other†	13 (7)	21 (6)
Age, y	45 (20-75)	45 (18-75)
Duration of psoriasis, y	19 (1-53)	19 (1-62)
Prior systemic psoriasis therapy, No. (%)		
Yes	139 (74)	283 (77)
No	48 (26)	86 (23)
PASI score	19 (11-50)	19 (10-59)
BSA affected by psoriasis, %	27 (10-90)	28 (10-95)
DLQI score	12 (0-30)	12 (0-30)
Itching VAS score	6 (0-10)	6 (0-10)
PSA frequency score	14 (2-24)	14 (2-24)
PSA severity score	15 (2-24)	15 (0-24)

Abbreviations: BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PSA, Psoriasis Symptom Assessment; VAS, Visual Analog Scale.
*Data are presented as mean (range) unless otherwise noted. Mean values have been rounded.
†Other includes persons who described their race/ethnicity as Asian or Pacific Islander, black, American Indian or Alaskan Native, or other.

Figure 2. Mean PASI Percentage Change Relative to Baseline Over the Study Period



PASI indicates Psoriasis Area and Severity Index. Error bars indicate SEMs. Asterisks indicate $P < .001$ for efalizumab vs placebo.

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for binomial outcome performed at the .05 level of significance: the proportion of patients who achieved an OLS rating of minimal or clear at week 12, the proportion of patients with PASI-50 at week 12 relative to day 0, and the proportion of patients who achieved a PGA rating of excellent or cleared at week 12. Using the 2-sided *t* test at the .05 significance level, mean improvement from baseline in the PASI thickness score at week 12 and mean improvement from baseline in the percentage of BSA affected by psoriasis at week 12 were compared. The PASI score and percentage of PASI improvement from baseline were summarized by time point. At each point, the mean percentage improvement from baseline was compared between the treatment groups using the *t* test. A hierarchical testing procedure determined the earliest point at which a statistically significant difference (at the .05 level) be-

Table 2. Improvement From Baseline in DLQI and PSA Severity Components*

	Baseline			Week 12		Improvement	
	No.	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
DLQI Components							
Symptoms and feelings							
Placebo	175	3.8 (1.6)	4 (3 to 5)	3.1 (1.6)	3 (2 to 4)	0.7 (1.6)	1 (0 to 2)
Efalizumab	346	4.0 (1.5)	4 (3 to 5)	2.0 (1.6)	2 (1 to 3)	1.9 (1.9)	2 (1 to 3)
Daily activities							
Placebo	172	2.5 (1.7)	2.5 (1 to 4)	2.2 (1.7)	2 (1 to 3)	0.3 (1.6)	0 (–1 to 1)
Efalizumab	347	2.5 (1.6)	2 (1 to 4)	1.4 (1.6)	1 (0 to 2)	1.1 (1.8)	1 (0 to 2)
Leisure							
Placebo	174	1.8 (1.8)	1 (0 to 3)	1.5 (1.6)	1 (0 to 2)	0.3 (1.6)	0 (0 to 1)
Efalizumab	345	1.8 (1.8)	1 (0 to 3)	0.8 (1.3)	0 (0 to 1)	1.0 (1.7)	0 (0 to 2)
Work and school							
Placebo	171	0.7 (0.9)	0 (0 to 1)	0.5 (0.8)	0 (0 to 1)	0.2 (0.8)	0 (0 to 0)
Efalizumab	335	0.8 (0.9)	1 (0 to 1)	0.3 (0.7)	0 (0 to 1)	0.4 (0.9)	0 (0 to 1)
Personal relationships							
Placebo	175	1.5 (1.7)	1 (0 to 2)	1.2 (1.6)	1 (0 to 2)	0.3 (1.3)	0 (0 to 1)
Efalizumab	346	1.4 (1.7)	1 (0 to 2)	0.7 (1.3)	0 (0 to 1)	0.7 (1.6)	0 (0 to 2)
Treatment							
Placebo	175	1.2 (1.1)	1 (0 to 2)	1.3 (1.0)	1 (1 to 2)	0 (1.0)	0 (–1 to 0)
Efalizumab	346	1.3 (1.0)	1 (0 to 2)	0.7 (0.8)	1 (0 to 1)	0.6 (1.1)	1 (0 to 1)
PSA Severity Subscales†							
Hurt							
Placebo	176	1.8 (1.0)	2 (1 to 3)	1.4 (1.0)	1 (1 to 2)	0.4 (1.0)	0 (0 to 1)
Efalizumab	343	1.8 (1.0)	2 (1 to 3)	0.8 (0.9)	1 (0 to 1)	0.9 (1.2)	1 (0 to 2)
Burning or stinging							
Placebo	176	1.7 (1.0)	2 (1 to 2)	1.4 (1.0)	1 (1 to 2)	0.3 (1.0)	0 (0 to 1)
Efalizumab	343	1.7 (1.0)	2 (1 to 3)	0.8 (0.9)	1 (0 to 1)	0.9 (1.2)	1 (0 to 2)
Itched							
Placebo	175	2.4 (0.8)	3 (2 to 3)	2.1 (0.9)	2 (1 to 3)	0.3 (0.8)	0 (0 to 1)
Efalizumab	338	2.4 (0.8)	3 (2 to 3)	1.3 (0.9)	1 (1 to 2)	1.1 (1.0)	1 (0 to 2)
Bothered by water							
Placebo	176	1.1 (1.1)	1 (0 to 2)	0.9 (1.0)	1 (0 to 2)	0.2 (1.0)	0 (0 to 1)
Efalizumab	342	1.1 (1.1)	1 (0 to 2)	0.6 (0.9)	0 (0 to 1)	0.5 (1.1)	0 (0 to 1)
Irritated							
Placebo	175	2.1 (0.9)	2 (2 to 3)	1.6 (0.9)	2 (1 to 2)	0.5 (0.9)	0 (0 to 1)
Efalizumab	343	2.0 (0.9)	2 (1 to 3)	1.0 (0.9)	1 (0 to 2)	1.0 (1.1)	1 (0 to 2)
Sensitive							
Placebo	175	1.9 (0.9)	2 (1 to 3)	1.6 (1.0)	1 (1 to 2)	0.3 (1.0)	0 (0 to 1)
Efalizumab	343	1.9 (1.0)	2 (1 to 3)	1.0 (1.0)	1 (0 to 1)	0.9 (1.1)	1 (0 to 2)
Skin condition bled							
Placebo	175	1.3 (0.9)	1 (1 to 2)	1.2 (0.9)	1 (0 to 2)	0.1 (0.9)	0 (0 to 1)
Efalizumab	343	1.3 (0.9)	1 (1 to 2)	0.6 (0.8)	0 (0 to 1)	0.7 (1.0)	1 (0 to 1)
Scaling							
Placebo	176	2.6 (0.6)	3 (2 to 3)	2.1 (0.9)	2 (1 to 3)	0.5 (0.9)	0 (0 to 1)
Efalizumab	344	2.5 (0.8)	3 (2 to 3)	1.2 (1.0)	1 (1 to 2)	1.3 (1.1)	1 (0 to 2)

Abbreviations: DLQI, Dermatology Life Quality Index; IQR, interquartile range; PSA, Psoriasis Symptom Assessment.
*P values calculated by 2-sample Wilcoxon rank sum test for between-group comparisons of improvement were <.001 for all comparisons.
†For this measure patients were asked to indicate how troubling/bothersome each listed symptom was during the previous 2 weeks.

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tween the treatment groups was observed. No multiple-comparison adjustment for the type I error was made in the hierarchical testing procedure, since there was no inflation of the type I error. To ensure an overall type I error rate of $\alpha = .05$ (2-sided) for all secondary efficacy analyses, the Hochberg-Bonferroni[31] multiple-comparisons procedure was used to adjust for multiple comparisons of secondary end points; all secondary end points retained statistical significance after multiplicity adjustments.

Mean improvements from baseline to week 12 on the overall DLQI and each of the 2 PSA scales were compared between treatment groups using the Wilcoxon rank sum test. The mean improvement from baseline in the Itching VAS at week 12 was compared between treatment groups using the *t* test. The overall scores and improvements from baseline for all patient-reported outcome scales were summarized by time point. At each point, the mean percentage improvement from baseline was compared between the treatment groups using the Wilcoxon rank sum test (DLQI and PSA) or *t* test (Itching VAS). A hierarchical testing procedure was used, as for efficacy.

RESULTS

Patient Characteristics

Between January and July 2002, 556 patients were enrolled at 30 study centers and randomized into the study, 369 patients into the 1-mg/kg-per-week efalizumab group and 187 patients into the placebo group (Figure 1). There were no statistically significant differences between the 2 treatment groups with respect to demographics, baseline characteristics, and disease severity (TABLE 1). The mean PASI score at baseline for the entire study cohort was 19, and mean BSA with psoriasis was 28% for the efalizumab-treated group and 27% for the placebo-treated group. The proportion of patients who did not complete treatment was similar in both groups (6.5% vs 6.4%); the most common reasons were patient decision (n=10), loss to follow-up (n=9), adverse event (n=9), use of an excluded medication (n=5), and investigator decision (n=3) (Figure 1). Four hundred seventeen patients (75%) received all 12 doses of assigned study drug.

Table 3. DLQI Improvement Stratified by PASI Response at Week 12

	PASI Improvement, %		
	≥75	51-74	≤50
	Placebo		
No. (%) of patients	8 (4)	18 (10)	157 (86)
Mean (SD) improvement	8.8 (5.5)	6.8 (5.7)	2.5 (6.5)
Median (IQR) improvement	8 (5 to 12)	5 (2 to 11)	2 (–1 to 6)
	Efalizumab		
No. (%) of patients	98 (27)	118 (32)	153 (41)
Mean (SD) improvement	8.8 (5.5)	6.8 (5.7)	2.5 (6.5)
Median (IQR) improvement	8 (5 to 12)	5 (2 to 11)	2 (–1 to 6)

Abbreviations: DLQI, Dermatology Life Quality Index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index.

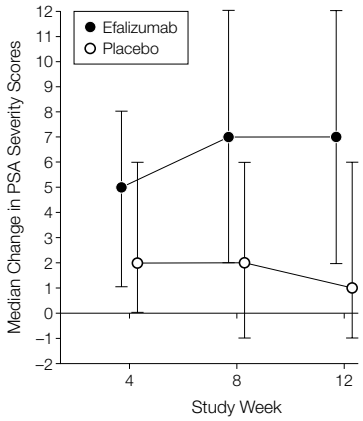
Treatment Efficacy

Physician-Assessed Outcomes. At the end of the 12-week treatment course, 27% of patients treated with efalizumab (98/369) achieved PASI-75 compared with 4% of patients who received placebo (8/187; $P<.001$). The treatment effect, defined as the difference in the proportion of patients who achieved PASI-75 between the efalizumab and placebo groups, was 22.3% (95% confidence interval, 15.8%-29.5%). Fifty-nine percent of efalizumab-treated patients (216/369) achieved PASI-50 compared with 14% of patients receiving placebo (26/187; $P<.001$). The mean PASI improvement at week 12 in the efalizumab-treated patients relative to baseline was about 52% compared with 19% in the patients who received placebo ($P<.001$) (FIGURE 2).

The proportion of patients with an OLS rating of minimal or clear at week 12 in the efalizumab group was significantly higher than that in the placebo group (26% vs 3%; $P<.001$). Similarly, the proportion of patients with a PGA rating of excellent or cleared at week 12 was significantly greater in the efalizumab group compared with the placebo group (33% vs 5%; $P<.001$).

Patient-Reported Outcomes. At week 12, the mean percentage improvement from baseline in DLQI overall score was greater in the efalizumab-treated group than in the placebo group (47% vs 14%; $P<.001$). Patients in the efalizumab-treated group showed improvement in mean DLQI scores compared with the placebo-treated group at 28 days ($P<.001$). Given the 1-week recall period associated with the DLQI, this difference in score between the 2 groups indicates that reduced dermatology-related limitations and improved functioning occurred fairly soon after initiating efalizumab therapy. There was a statistically significant trend toward a positive efalizumab treatment effect across all DLQI components (TABLE 2), with the greatest difference between the treatment groups at week 12 observed in the "symptoms and feelings" domain (48% vs 18%). Additional analy-

Figure 3. Median Change in PSA Severity Relative to Baseline Over the Study Period



PSA indicates Psoriasis Symptom Assessment. Error bars indicate interquartile ranges.

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Table 4. Adverse Events Occurring in at Least 5% of All Patients

Adverse Events	No. (%) of Patients: Placebo (n = 187)	No. (%) of Patients: Efalizumab (n = 368)*	*P* Value†
Total‡	133 (71)	296 (80)	.02
Headache	39 (21)	123 (33)	.002
Infection, not otherwise specified	23 (12)	46 (13)	>.99
Chills	10 (5)	44 (12)	.01
Nausea	13 (7)	39 (11)	.22
Myalgia	8 (4)	38 (10)	.01
Pain	9 (5)	37 (10)	.03
Pharyngitis	10 (5)	27 (7)	.47
Flulike syndrome	7 (4)	27 (7)	.13
Fever	3 (2)	25 (7)	.007
Rhinitis	11 (6)	23 (6)	>.99
Asthenia	9 (5)	22 (6)	.70
Diarrhea	10 (5)	20 (5)	>.99
Unintentional injury	19 (10)	17 (5)	.02

*Excludes 1 patient who was randomized but discontinued before receiving any study drug.
†*P* values were calculated using a 2-sided Fisher exact test for binomial distributions.
‡Patients with at least 1 adverse event.

ses showed the summary statistics on DLQI improvement stratified by PASI response at week 12 in the 369 patients who were randomized to receive efalizumab, with the greatest improvement observed in the patients who achieved PASI-50 (TABLE 3).

When patients with a baseline Itching VAS score of 0 (9 patients in the efalizumab group and 3 in the placebo group) were excluded from the analysis, efalizumab treatment was shown to produce a 38% improvement in Itching VAS score, compared with a slight worsening in score (–0.2%) in the placebo group at 12 weeks ($P<.001$). A significant improvement in the mean Itching VAS in the efalizumab group relative to the placebo group was observed at the first time point measured ($P<.001$).

Comparisons of the mean percentage improvement from baseline in the efalizumab group vs the placebo group were statistically significant for both frequency of symptoms (48% vs 18%; $P<.001$) and severity of symptoms (eg, troubling or bothersome) (47% vs 17%; $P<.001$). Improvement in both mean PSA frequency and mean PSA severity subscale scores was evident in the efalizumab group vs the placebo group at the first time point at which PSA was measured ($P<.001$) (FIGURE 3). There was a trend toward improvement across all symptoms in both frequency and severity in the efalizumab group, as evidenced by the mean improvement in PSA scores (Table 2). With respect to the frequency of symptoms, differences between absolute improvements were similar for most symptoms (itching, irritation, sensitivity, bleeding, and scaling). With respect to severity, or how bothersome the symptoms were, the largest absolute improvements occurred in both the itching (mean improvement of 1.1 for efalizumab vs 0.3 for placebo; $P<.001$) and scaling (1.2 for efalizumab vs 0.4 for placebo; $P<.001$) components.

Safety Evaluation

Efalizumab therapy was generally well tolerated. All adverse events that occurred in at least 5% of all patients are shown in TABLE 4. Five types of adverse events (headache, chills, fever, myalgia, and pain) occurred at least 5% more frequently in the efalizumab group than in the placebo group. These events tended to be a portion of the complex of mild to moderate flulike symptoms that occur following the first 1 to 2 injections of efalizumab.

Serious adverse events were infrequent, occurring in 2% of efalizumab-treated patients (9/368) and 1% of placebo-treated patients (1/187). No deaths were reported for patients during the study. Fourteen patients (3%) (12 [3%] in the efalizumab group and 2 [1%] in the placebo group) experienced adverse events that resulted in withdrawal of study drug.

No clinically significant laboratory abnormalities or pattern of changes in vital signs were observed during efalizumab treatment. Eight patients (2%) developed positive antibodies to efalizumab after exposure to the drug. None of these patients experienced serious adverse events or discontinued treatment. No patients in the placebo group developed anti-efalizumab antibodies.

The rate of diagnosed infections was 27% for the efalizumab group and 23% for the placebo group. Infections that occurred at least 1% more frequently in the efalizumab-treated patients than in the placebo-treated patients included mild to moderate viral infection (primarily mild to moderate viral upper respiratory tract infections), bacterial infection (eg, impetigo, streptococcal pharyngitis), cellulitis, and fungal (yeast) infection. Infections graded as severe occurred in 0.5% of patients in both the efalizumab and placebo groups. Efalizumab-treated patients did not exhibit increased susceptibility to any one type of pathogen, nor was there evidence of infection characteristic of opportunistic infections observed in immunocompromised hosts.

No cases of anaphylaxis were observed during efalizumab therapy. During the study, 2 cases of malignancy were diagnosed (1 case each of squamous cell cancer at day 2 and basal cell cancer at day 77) in efalizumab-treated patients, although neither was judged as being related to efalizumab by investigators.

COMMENT

Limitations of currently available psoriasis therapies highlight the need for effective and safe treatment options. Traditional systemic therapies are associated with cumulative toxic effects, potentially increasing the risk of end-organ

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damage or malignancy.[32,33] In this phase 3 randomized, placebo-controlled trial, efalizumab therapy resulted in significant improvement in the primary end point and other prespecified efficacy end points. The efficacy, accompanied by the safety profile and the HRQL outcomes, provides evidence of potential benefit for efalizumab in patients with psoriasis. By week 12, 27% of efalizumab-treated patients achieved a PASI-75 response compared with 4% of placebo-treated patients. These results are consistent with the physician-reported outcomes from another recently reported trial of efalizumab.[34] Efalizumab-treated patients demonstrated significant benefit on the additional physician-assessed global psoriasis scales, OLS and PGA, compared with placebo-treated patients. Consistent and significant improvements on multiple dermatology- and psoriasis-specific patient-reported end points were observed throughout the study.

The magnitude of the percentage improvement in HRQL was greater than that for PASI in the early stage of treatment. Improvement in the individual PASI components occurred early; however, it is likely that the BSA component, which improves less rapidly, underestimates the improvement occurring in the lesions. This suggests that concentrating solely on PASI improvement might underestimate the timing and overall response to efalizumab.

Efalizumab treatment reduced the frequency and severity of psoriasis symptoms, particularly in the severity of itching and scaling, the 2 most frequently reported subjective symptoms.[3] The severity and frequency of other symptoms, including bleeding and burning or stinging, also were improved by efalizumab treatment. The significant improvement on the DLQI indicated consistent improvements across measures of social and mental assessment (Table 2), areas known to be adversely affected in patients with psoriasis. Efalizumab-treated patients reported greater improvement in their attitudes about their disease, their ability to participate in daily activities (including leisure and work), and their personal relationships, and they reported fewer treatment-related problems compared with placebo.

Efalizumab exhibited a favorable safety profile and was generally well tolerated. The most commonly occurring adverse events during the initiation of efalizumab treatment were mild to moderate flulike symptoms following the first 1 to 2 injections. Serious adverse events were infrequent and occurred at only a slightly greater frequency in the efalizumab group (2%) than in the placebo group (1%). There was no evidence to suggest clinically relevant increases in either infection or malignancy, including lymphoma, among efalizumab-treated patients; however, longer follow-up will be needed to accurately characterize the risk of infection and malignancy.

There were no clinically relevant laboratory abnormalities. Previous efalizumab studies in psoriasis patients have shown that the discrete elevations in lymphocyte counts, white blood cell counts, and other hematologic parameters are transient, usually within normal ranges, with values returning to baseline following efalizumab discontinuation.[35-37] There was no evidence of general systemic toxicity reflected by changes in hepatic or renal function.

This investigation is limited by the relatively short duration and by lack of an active comparator. Since psoriasis is a chronic disease, outcomes with longer-term use of efalizumab are important. The efficacy and safety of longer-term efalizumab treatment has been further evaluated in an extension of this study that analyzes up to 24 weeks of continuous efalizumab therapy. The preliminary analysis of data from this study suggests continued improvement in disease severity and maintenance of safety. Additionally, an ongoing open-label study evaluating the efficacy and safety of up to 3 years of continuous efalizumab therapy is currently being conducted. Efficacy with continued use of efalizumab has also been suggested in a recently reported clinical trial.[34] The current study did not compare efalizumab directly with any of the currently used therapies for psoriasis. Additional randomized studies would be needed to compare this profile with other currently available therapies.

Efalizumab was recently approved for treatment of patients with chronic moderate to severe plaque psoriasis.[38] The benefit across physician-assessed end points and multiple patient-reported measures of HRQL observed in this study along with the favorable safety profile suggest that efalizumab could provide a viable treatment option for patients with moderate to severe plaque psoriasis.

Author Contributions: Dr Gordon had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Gordon, Papp, Walicke, Dummer, Bresnahan.
Acquisition of data: Gordon, Papp, Hamilton, Dummer.
Analysis and interpretation of data: Gordon, Papp, Walicke, Dummer, Li, Bresnahan, Menter.
Drafting of the manuscript: Gordon, Dummer, Li, Bresnahan.
Critical revision of the manuscript for important intellectual content: Gordon, Papp, Hamilton, Walicke, Dummer, Li, Bresnahan, Menter.
Statistical expertise: Gordon, Li.
Obtained funding: Papp.
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ring, MD, University of Texas Medical Branch, Houston; Michael D. Zanolli, MD, Dermatology Consultants, Nashville, Tenn.

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rorism agents. Examining each of the 6 diseases individually, the percentage of jurisdictions that mandate reporting ranged from a low of 44% (viral hemorrhagic fevers) to a high of 100% (anthrax, botulism).

Comment. To our knowledge, this is the first description of the use of the Web by states and territories for reporting of infectious diseases. Our results indicate that while most jurisdictions maintain Web sites, many did not clearly describe what, when, how, and where health care providers should report diseases. We also found considerable variation in Web-based information on reporting requirements for diseases potentially related to bioterrorism. Including explicit requirements to report all Category A diseases on a jurisdiction's reportable disease list not only reduces uncertainty about what is reportable, but also raises awareness of these threats.[5,6]

Because most jurisdictions already maintain Web sites, updating them to provide complete, accessible disease reporting information should be relatively inexpensive. More effective use of the Web could strengthen the partnership among clinicians and local public health officials that is vital for recognition of and response to disease outbreaks and bioterrorism-related events.

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CORRECTION

Incorrect Table: In the Original Contribution entitled "Efaluzimab for Patients With Moderate to Severe Plaque Psoriasis: A Randomized Controlled Trial" published in the December 17, 2003, issue of THE JOURNAL (2003;290:3073-3080), Table 2 contained erroneous numbers for mean (SD) and median (IQR) placebo group improvement; additionally, erroneous PASI improvement percentage headings were shown. The correct table is shown below.

Table 3. DLQI Improvement Stratified by PASI Response at Week 12

	PASI Improvement, %		
	≥75	50-74	<50
	Placebo		
No. (%) of patients (n = 183)*	8 (4)	18 (10)	157 (86)
Mean (SD) improvement	6.5 (5.4)	8.2 (7.1)	0.6 (4.9)
Median (IQR) improvement	5.5 (3 to 10.5)	6.5 (4 to 13)	1 (–2 to 3)
	Efalizumab		
No. (%) of patients (n = 363)*	97 (27)	117 (32)	149 (41)
Mean (SD) improvement	8.8 (5.5)	6.8 (5.7)	2.5 (6.5)
Median (IQR) improvement	8 (5 to 12)	5 (2 to 11)	2 (–1 to 6)

Abbreviations: DLQI, Dermatology Life Quality Index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index.
*Data are derived from the number of patients for whom values were available.

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