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Safety of Efalizumab Therapy in Patients with Moderate to Severe Psoriasis

An Open-Label Extension of a Phase IIIb Trial

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Abstract

Background: Psoriasis is a chronic autoimmune disease characterized by infiltration of the dermis and epidermis by activated T cells and the hyperproliferation and abnormal differentiation of keratinocytes. It is a life-long disease with alternating periods of remission and recurrence. Efalizumab is a humanized, recombinant, T-cell targeting monoclonal antibody, approved for use in adults with chronic moderate to severe plaque psoriasis.

Objective: To assess the safety of continued or newly initiated treatment with efalizumab for up to 48 weeks in patients with psoriasis who were treated previously with efalizumab or placebo.

Methods: This study was an open-label, 48-week extension of a previously published 12-week, randomized, double-blind, parallel-group, placebo-controlled, multicentre, phase IIIb study, carried out in the US and Canada between 24 October 2002 and 2 July 2004. Patients were followed and treated at the study clinic in an outpatient setting and also were trained to self-administer the drug at home. Patients comprising individuals with chronic moderate to severe plaque psoriasis who had completed the 12-week, placebo-controlled segment of the study were eligible for enrolment in the extension phase. Of the 686 patients enrolled in the study, 636 (92.7%) enrolled in the open-label extension of the study, 418 of whom had received 12 weeks of efalizumab therapy and 218 of whom had received 12 weeks of placebo. All patients entering the open-label phase of the study received efalizumab 1 mg/kg/wk for an additional 48 weeks, for a maximum exposure of up to 60 weeks. Safety was evaluated by an assessment of adverse events, including infections and serious adverse events.

Results: The rate of withdrawal due to adverse events remained low throughout the trial, ranging from 1.2% to 6.6% during the 12-week segments of the open-label extension phase of the trial. The incidence of adverse events decreased with increased exposure to efalizumab; the incidence during the initial 12 weeks of

exposure to efalizumab was 79.0% compared with 72.9% for patients exposed to placebo. Patients treated with efalizumab for 13–24 weeks, 25–36 weeks, 37–48 weeks and 49–60 weeks experienced adverse events at an incidence of 66.8%, 54.3%, 49.6% and 48.5%, respectively. The incidence of serious adverse events ranged from 1.6% to 3.5% during the 12-week segments of efalizumab therapy, compared with an incidence of 3.4% for placebo-treated patients. The incidence of infection ranged from 9.9% to 14.7% during the 12-week segments of efalizumab therapy, compared with an incidence of 19.1% for placebo-treated patients. Malignancies were reported with an incidence of ≤1.0% for efalizumab-treated patients during any 12-week segment compared with 0.4% for the 12-week placebo-treated patients. Of the 15 malignancies reported for efalizumab-treated patients, 13 were basal cell (n = 4) or squamous cell (n = 9) carcinomas.

Conclusions: These results support the short-term safety profile demonstrated for efalizumab over a longer-term therapy period of up to 60 weeks.

Background

Psoriasis is a chronic autoimmune disorder characterized by abnormal keratinocyte differentiation and hyperproliferation, and an aberrant inflammatory process in the dermis and epidermis. It is a life-long inflammatory disease that typically begins in late adolescence or early adulthood.[1]

Although numerous conventional therapies have been effective for the treatment of symptoms, the risk of toxicity restricts their long-term use. Many of the conventional agents are immunosuppressants and, as such, increase the potential risk of infection. Additionally, serious adverse events have been associated with long-term use of these therapies, including hepatotoxicity (methotrexate and acitretin); teratogenicity (acitretin); renal toxicity and hypertension (ciclosporin); and nausea, pruritus and skin cancer (psoralen with ultraviolet A [PUVA] phototherapy).[2-7]

Several other approaches to monotherapy have been developed for managing psoriasis symptoms that limit the exposure to and cumulative toxicity of these agents, including rotational, combination and sequential therapies.[8-13] However, despite these approaches, satisfactory life-long management of psoriasis with minimal toxic effects remains a clinical challenge.

Recent advances in understanding the immunopathogenesis of psoriasis have led to the development of targeted biological therapies with the expectation that these agents would afford reduced toxicity and allow for long-term treatment. Five agents have been developed and can be divided into two classes according to their mechanism of action. Etanercept, infliximab and adalimumab are agents that target tumour necrosis factor-α, a cytokine mediator of the inflammatory process. Alefacept and efalizumab target T-cell interactions, processes that are central to the immunopathogenesis of psoriasis.

Efalizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody that binds to the CD11a subunit of lymphocyte function-associated antigen (LFA-1), preventing LFA-1 binding to intercellular adhesion molecules (ICAM-1). The interaction of LFA-1 with ICAM-1 is essential for the activation and infiltration of T lymphocytes and dendritic cells into the dermis and epidermis,[14] and is a key step in the cascade of events that occurs during the pathogenesis of psoriasis. Efalizumab is indicated for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

A short-term placebo-controlled trial investigated safety and tolerability of efalizumab for 12 weeks in patients with moderate to severe plaque psoriasis.[15] Here, we report the results of an extension to that study.

Methods

Study Design

This 48-week, open-label study, protocol ACD2601g, is an extension of a previously published 12-week randomized, double-blind, parallel-group, placebo-controlled, multicentre phase IIIb study carried out at 58 treatment centres in the US and Canada.[15] That study population comprised adults with a diagnosis for at least 6 months duration of plaque psoriasis that covered ≥10% of body surface area and a Psoriasis Area and Severity Index (PASI) score of ≥12.0 at screening, who were candidates for or had previously been treated with systemic psoriasis therapy.

In the 12-week study,[15] patients were randomized to receive efalizumab 1 mg/kg/wk or placebo for 12 weeks. Acute influenza-like symptoms sometimes accompanied the first or second dose, but the frequency of acute adverse events with efalizumab use was comparable to that with placebo by the third and all subsequent doses. No evidence of end-organ toxicity or increased risk of infection was seen with efalizumab therapy.

The 12-week study[15] included a 4-week screening period that also served as a washout period. During this washout period, concomitant therapies were not allowed, with the exception of emollients, tar or salicylic acid for scalp psoriasis, and small amounts of potency group VI or VII topical corticosteroids for psoriatic lesions on the face, hands, feet, groin or axillae. On day 0 of this initial study, patients were randomized and administered a 0.7 mg/kg conditioning dose of efalizumab or placebo equivalent, followed by 11 weekly efalizumab doses of 1 mg/kg.

At the end of the 12-week study,[15] patients who completed the study from both the efalizumab and placebo groups were given the opportunity to enter an open-label extension phase to receive efalizumab (Raptiva®[1]; Genetech, Inc., South San Francisco, CA, USA) 1 mg/kg/wk for up to four 12-week treatment segments. During the extension period, which was carried out between 24 October 2002 and 2 July 2004, the primary objective was to assess the safety of efalizumab with continuous treatment.

During the first extended treatment (ET) segment of the extension phase, each patient, including those who had received efalizumab during the placebo-controlled phase of the study, received a conditioning dose of 0.7 mg/kg efalizumab, followed by 11 weekly doses of 1 mg/kg. During ET segments 2, 3 and 4, patients received 12 weekly efalizumab doses of 1 mg/kg.

Patient Selection

In addition to having completed the 12-week, randomized, double-blind, placebo-controlled study,[15] an additional inclusion criterion for the extension study was that women of childbearing potential should continue to use an acceptable method of contraception for the duration of the study. Patients who discontinued early during the course of the 12-week randomized, double-blind study were considered ineligible and were not allowed to transfer to the extension study.

Concomitant Therapies

Patients were allowed the use of all emollients, scalp preparations, topical psoriasis therapies (e.g. corticosteroids, coal tar preparations, dithranol, calcipotriol, and topical retinoids) and phototherapy (e.g. ultraviolet B, ultraviolet A or PUVA) at any time during the ET period. These concomitant therapies could be used alone or in combination. During the ET period, systemic treatments for psoriasis, immunosuppressive medications for any indication other than psoriasis, and concomitant experimental drugs or treatments were not allowed. The use of live virus or bacteria vaccines was also prohibited during the ET period.

Treatment Schedule and Assessments

The overall treatment and assessment schedule is presented diagrammatically in figure 1. Patients were trained for self-administration at home during

1 The use of trade names is for product identification purposes only and does not imply endorsement.

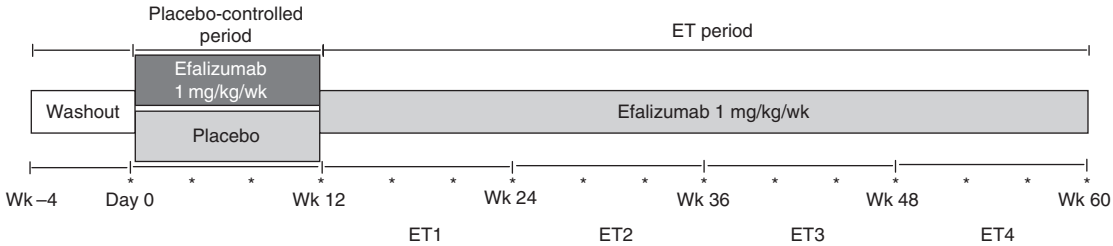

Fig. 1. Study design. At day 0, patients in the efalizumab arm of the study received a conditioning dose of 0.7 mg/kg followed by weekly doses of 1.0 mg/kg. At entry to extended treatment (ET), all patients received a conditioning dose of 0.7 mg/kg, followed by weekly doses of 1.0 mg/kg.

the first ET segment (ET1) on days 0, 7 and 14 (i.e. the beginning of weeks 0, 1 and 2) and were allowed to self-administer efalizumab at weeks 3, 5, 6, 7, 9, 10 and 11. At weeks 0, 1, 2, 4 and 8, patients were weighed and dosages were calculated. At weeks 1, 2, 4 and 8, the use of concomitant medications was reviewed and recorded and adverse events were monitored and recorded. At weeks 4 and 8, the patients were observed during self-administration of efalizumab in order to check on compliance.

At week 12 (i.e. the conclusion of the ET1 segment), each patient underwent a physical examination, including a dermatological examination. A Psoriasis Symptom Assessment was taken, and PASI score was recorded. Vital signs were recorded; a blood sample was drawn for haematology, serum chemistry and antibody assessments, and urine was collected for urinalysis and a pregnancy test (for women of childbearing potential only).

At weeks 4 and 8 of each subsequent ET segment, patients returned to the study site for bodyweight measurements and dose calculations and for reviewing and recording of concomitant medication use and adverse events. A urine pregnancy test was administered to female patients of childbearing potential. Patients were given the option to self-administer the drug and were observed while self-administering a dose of efalizumab. At weeks 0, 2, 3, 5, 6, 7, 9, 10 and 11 of each subsequent ET segment (ET2, ET3 and ET4), the patients who chose to do so self-administered efalizumab 1 mg/kg. At week 12 of each segment, all patients underwent the same examination as described for ET1. Because week 12 for each segment was also week 0 of the next segment, patients followed both week 12 and week 0 schedules, with the exception of week 12 of ET4, when the study period terminated.

At week 12 of ET4, patients were given the option of entering a treatment-free follow-up period or continuing to receive an additional 12 weeks of efalizumab 1 mg/kg/wk. Patients in the US had the option of continuing efalizumab treatment to day 77 of the follow-up period, or until the drug became commercially available, whichever occurred first.

Statistical Analysis

Adverse events were assessed based on the patient's total length of exposure to efalizumab during both the 12-week randomized, double-blind, placebo-controlled study and during the open-label extension study. For example, a patient who had received efalizumab during the 12-week, placebo-controlled study[15] and continued to receive efalizumab during four ET segments of the extension study would have been exposed to efalizumab for a total of 60 weeks. A patient who had received placebo during the 12-week, placebo-controlled study and then transferred to the extension study and received efalizumab for four ET segments would have been exposed to efalizumab for a total of 48 weeks. Confidence intervals were determined using the Clopper-Pearson interval method based on an F-distribution.

The primary endpoint of the study was safety. Safety analyses were based on the number of patients who received any amount of study drug according to the actual treatment received. Summaries

Table I. Baseline[a] demographic and psoriasis characteristics of patients entering the efalizumab extension study

Characteristic	Placebo-controlled randomized segment		Open-label extension
	placebo (n = 236)	efalizumab (n = 450)	(n = 636)
Sex [n (%)]			
men	140 (59.3)	303 (67.3)	416 (65.4)
women	96 (40.7)	147 (32.7)	220 (34.6)
Age (years)			
mean (SD)	46.4 (12.1)	45.6 (12.5)	45.9 (12.2)
median (range)	46 (20–77)	45 (18–74)	46 (18–77)
History of systemic therapy [n (%)]	174 (73.7)	328 (72.9)	462 (72.6)
Duration of psoriasis (years)			
mean (SD)	17.5 (11.1)	18.5 (12.1)	18.3 (11.7)
median (range)[b]	17 (<1–50)	16 (<1–68)	16 (<1–68)
Psoriasis Area and Severity Index			
mean (SD)	18.7 (7.0)	19.1 (7.5)	18.1 (8.1)
median (range)	16.7 (10.5–49.6)	16.8 (10.2–54.6)	16.2 (1.6–60.3)
Affected body surface area (%)			
mean (SD)	26.8 (15.2)	27.7 (15.8)	27.1 (15.6)
median (range)	22 (10–83)	23 (10–85)	22 (10–85)

a Baseline for listed variables was day 0 of the treatment period in which patients were first exposed to efalizumab except for the duration of psoriasis and history of systemic therapy, which were based on day 0 of the earlier 12-wk placebo-controlled study.

b One patient treated initially with placebo and another treated initially with efalizumab had psoriasis for <1 year (one 6 months, one 4 months), a protocol violation.

of adverse events, deaths, laboratory test results, vital signs and anti-efalizumab antibodies were produced for each 12-week treatment period, and analyses were performed based on the length of exposure to efalizumab.

The number of patients enrolled in the extension study was dependent upon the number of patients who completed the initial 12-week,[15] placebo-controlled study. The sample size in that study was based on safety considerations such that there would be a high probability of observing one or more instances of an adverse event with a background rate of 1% or 2% over a 12-week period. A total of 686 patients enrolled in the placebo-controlled study, and 636 patients transferred to the extension study.

Results

Baseline Characteristics of the Study Population

Baseline characteristics are summarized in table I. At enrolment in ET1, patients had a prior diagnosis of moderate to severe plaque psoriasis of long-standing duration with a median of 16 years and a range of <1–68 years (mean ± SD, 18.3 ± 11.7). The median PASI score at the time of entry to the open-label portion of this study was 16.2 with a range of 1.6–60.3 (mean ± SD, 18.1 ± 8.1). More than two-thirds of the patients had a history of systemic psoriasis therapy.

Patient Disposition

The initial 12 weeks of the study were the placebo-controlled period, and a total of 686 patients were randomized to receive efalizumab 1 mg/kg/wk (n = 450) or placebo (n = 236).[15] Completion of the placebo-controlled period was required for eligibility to enter the open-label 48-week ET period; 639 patients (93.1%) completed the placebo-controlled period. Of the 686 patients enrolled in the initial study, 636 (92.7%) enrolled in the open-label extension of the study; 418 patients had received 12 weeks of efalizumab therapy, and 218 patients had received 12 weeks of placebo. A total of 449 (70.6%) patients completed 48 weeks of extended treatment. As a result, 293 patients had received

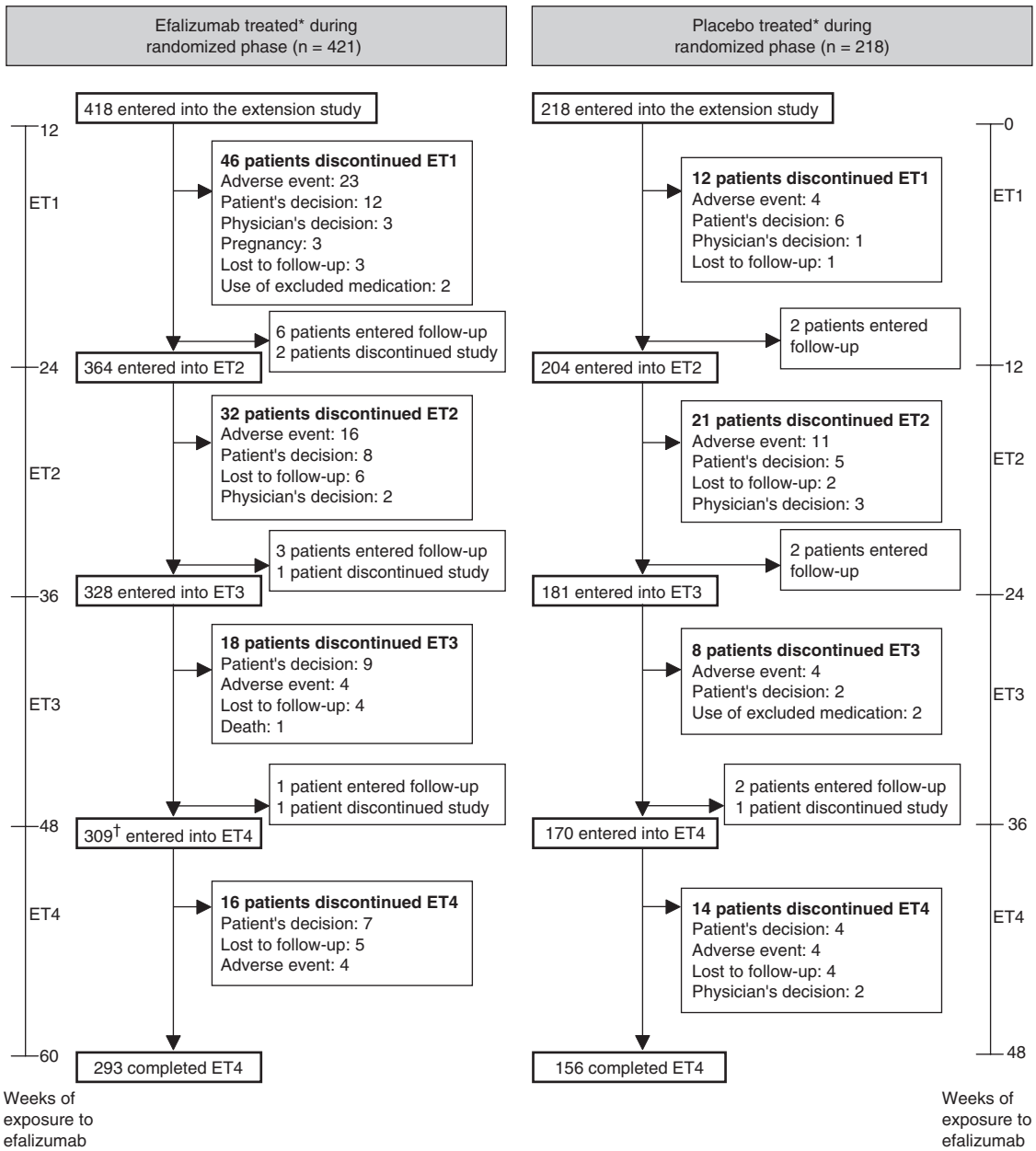

Fig. 2. Disposition of patients during the extended study segments. * Patients completing treatment during the randomized, placebo-controlled phase. **ET** = extended treatment. † One patient who originally intended to discontinue during ET3 continued treatment in ET4.

a total of 60 weeks, and 156 patients a total of 48 weeks of continuous efalizumab therapy. The disposition of the patients is summarized in figure 2.

Over the course of the open-label extension study, 188 of 636 patients (29.6%) discontinued early, of whom 82 (43.6%) withdrew because of an adverse event, including an additional 12 cases that

were identified through a thorough clinical review as potential discontinuation due to an adverse event. These included 18 events of arthralgia or arthritis, 15 events of psoriasis and 4 events of leukopenia; all other adverse events that led to withdrawal occurred at a frequency of three or fewer events. Patients also withdrew due to lack of efficacy (43 patients, 22.9%) or were lost to follow-up (25 patients, 13.3%); 38 patients (20.2%) discontinued for other reasons: initiation of excluded medication (10 patients), noncompliance (6 patients), relocation (4 patients), pregnancy (3 patients), withdrawal of consent (2 patients) or other reasons (13 patients).

Safety

Efalizumab was well tolerated during up to 60 weeks of continuous administration. In the placebo-controlled, randomized, double-blind phase of the study, the overall incidence of adverse events during the 12-week treatment period was 82.2% and 72.9% in the efalizumab- and placebo-treated groups, respectively.[15] For all patients exposed to efalizumab during the controlled and extension periods for up to 12 weeks, the incidence of adverse events was 79.0%. The adverse events occurring in ≥5% of patients during any one segment and categorized by exposure to drug are summarized in table II.

Most of the adverse events reported during the first 12 weeks of efalizumab exposure were acute adverse events, prospectively defined as headache, fever, chills, nausea, vomiting or myalgia occurring within 2 days after administration of the study drug. Acute adverse events occurred most frequently after the first efalizumab dose in 16.7% of patients receiving their first exposure to efalizumab in the ET period, and declined in frequency with the second dose; by the third dose, the rate was comparable with that of patients receiving placebo in the earlier placebo-controlled study.

During the 12-week randomized, placebo-controlled, double-blind phase of the study, 44.1% and 26.7% of efalizumab- and placebo-treated patients, respectively, experienced adverse events considered by the investigator to be potentially related to the study drug.[15] Adverse events considered to be related to the study drug that occurred in the open-label extension are presented according to duration of exposure in table III. The overall incidence of adverse events and study drug-related adverse events did not increase with additional treatment during 60 weeks of continuous efalizumab therapy (table II and table III). No new common adverse events occurring in ≥5% of patients were reported with extended efalizumab exposure.

The incidence of clinically important adverse events (including the incidence of serious adverse events, diagnosed infections, psoriasis adverse events, arthritis adverse events and malignancy) was comparable in each 12-week segment of the extended efalizumab treatment period to that observed in the placebo-controlled, randomized, double-blind phase of the study and remained generally stable with increased exposure to efalizumab (table IV).

The incidence of psoriasis-related adverse events remained consistent over any given 12-week ET segment, ranging between 2% and 3%. Eight patients experienced severe psoriasis-related adverse events; four of these patients withdrew from treatment.

The incidence of arthritis-related adverse events remained low and consistent over each 12-week ET segment, rising to 1% above the rate seen in the placebo-treated group only during 49–60 weeks of treatment. During this final segment, arthritis-related adverse events were reported for seven patients; two of the seven patients reported a history of psoriatic arthritis. A total of 15 patients withdrew from treatment as a result of psoriatic arthritis-related adverse events; eight events were classified as severe, six as moderate and one as mild.

Reported malignancies were categorized into two groups: non-cutaneous solid tumours and non-melanoma skin cancer (NMSC). Three non-cutaneous solid tumours were reported. One case each of gastrointestinal carcinoma, breast cancer and a neuroendocrine carcinoid tumour was reported during weeks 13–24, 25–36 and 49–60 weeks of exposure, respectively, and none of these tumours was deemed related to the study drug. Thirteen diagnoses of NMSC in 11 patients were reported throughout the

Table II. Adverse events occurring in ≥5% of patients during any 12-wk period of the placebo-controlled and open-label extension treatment phases[a]

Adverse event[b]	Placebo [% (95% CI)]	Duration of exposure to efalizumab [% (95% CI)]				
	wk 1–12[c] (n = 236)	wk 1–12 (n = 666)	wk 13–24 (n = 622)	wk 25–36 (n = 545)	wk 37-48 (n = 498)	wk 49-60 (n = 309)
All adverse events[d]	72.9 (66.7, 78.4)	79.0 (75.7, 82.0)	66.8 (63.0, 70.5)	54.3 (50.0, 58.6)	49.6 (45.1, 54.1)	48.5 (42.8, 54.3)
Headache	16.9 (12.4, 22.4)	27.0 (23.7, 30.6)	5.3 (3.7, 7.4)	3.5 (2.1, 5.4)	2.6 (1.4, 4.4)	2.6 (1.1, 5.0)
Infection NOS	19.1 (14.3, 24.7)	14.7 (12.1, 17.6)	14.2 (11.5, 17.2)	9.9 (7.5, 12.7)	13.1 (10.2, 16.3)	13.9 (10.3, 18.3)
Chills	3.8 (1.8, 7.1)	9.3 (7.2, 11.8)	0.5 (0.1, 1.4)	0.2 (0.0, 1.0)	0.0 (0.0, 0.7)	1.0 (0.2, 2.8)
Influenza-like symptoms	5.5 (3.0, 9.2)	9.3 (7.2, 11.8)	3.7 (2.4, 5.5)	1.5 (0.6, 2.9)	2.8 (1.5, 4.7)	3.6 (1.8, 6.3)
Nausea	4.7 (2.3, 8.2)	7.8 (5.9, 10.1)	1.6 (0.8, 2.9)	0.4 (0.0, 1.3)	0.2 (0.0, 1.1)	0.3 (0.0, 1.8)
Pharyngitis	7.2 (4.3, 11.3)	7.7 (5.8, 9.9)	4.3 (2.9, 6.3)	3.1 (1.8, 4.9)	2.6 (1.4, 4.4)	4.2 (2.3, 7.1)
Myalgia	5.9 (3.3, 9.8)	6.8 (5.0, 8.9)	2.1 (1.1, 3.6)	0.7 (0.2, 1.9)	0.8 (0.2, 2.0)	0.6 (0.1, 2.3)
Rhinitis	5.5 (3.0, 9.2)	6.3 (4.6, 8.4)	5.5 (3.8, 7.6)	1.3 (0.5, 2.6)	1.6 (0.7, 3.1)	2.3 (0.9, 4.6)
Sinusitis	8.5 (5.3, 12.8)	6.2 (4.5, 8.3)	5.3 (3.7, 7.4)	3.3 (2.0, 5.2)	2.4 (1.3, 4.2)	1.9 (0.7, 4.2)
Generalized pain	3.8 (1.8, 7.1)	6.0 (4.3, 8.1)	3.7 (2.4, 5.5)	4.0 (2.5, 6.0)	2.6 (1.4, 4.4)	1.9 (0.7, 4.2)
Diarrhoea	6.4 (3.6, 10.3)	4.2 (2.8, 6.0)	1.4 (0.7, 2.7)	0.9 (0.3, 2.1)	0.6 (0.1, 1.8)	0.6 (0.1, 2.3)
Pruritus	7.2 (4.3, 11.3)	3.6 (2.3, 5.3)	2.1 (1.1, 3.6)	1.3 (0.5, 2.6)	0.4 (0.0, 1.4)	0.3 (0.0, 1.8)

a The placebo-treated patients from the preliminary 12-wk segment of this trial[15] are included for comparison purposes.

b Patients who experienced at least one adverse event of the type described. The same patient may be counted in multiple categories.

c The incidence of adverse events in the placebo group during the randomized treatment phase; 218 of these patients went on to start efalizumab treatment and are included in the subsequent treatment columns.

d Patients who experienced at least one adverse event while exposed to efalizumab, irrespective of its perceived relationship with the study drug.

NOS = not otherwise specified; primarily colds and upper respiratory tract infections.

Table III. Adverse events related to study drug occurring in ≥1% of patients during any 12-wk period of the placebo-controlled and open-label extension treatment phases[a]

Adverse event[b]	Placebo [% (95% CI)]	Duration of exposure to efalizumab [% (95% CI)]				
	wk 1–12[c] (n = 236)	wk 1–12 (n = 666)	wk 13–24 (n = 622)	wk 25–36 (n = 545)	wk 37–48 (n = 498)	wk 49–60 (n = 309)
All adverse events[d]	26.7 (21.2, 32.8)	38.0 (34.3, 41.8)	12.6 (10.1, 15.4)	5.7 (3.9, 8.0)	5.4 (3.6, 7.8)	2.9 (1.3, 5.5)
Headache	11.0 (7.3, 15.7)	18.2 (15.3, 21.3)	1.0 (0.4, 2.1)	0.2 (0.0, 1.0)	0.4 (0.0, 1.4)	0.6 (0.1, 2.3)
Chills	2.5 (0.9, 5.5)	8.4 (6.4, 10.8)	0.2 (0.0, 0.9)	0.0 (0.0, 0.7)	0.0 (0.0, 0.7)	0.3 (0.0, 1.8)
Influenza-like symptoms	0.8 (0.1, 3.0)	4.5 (3.1, 6.4)	0.6 (0.2, 1.6)	0.0 (0.0, 0.7)	0.0 (0.0, 0.7)	0.3 (0.0, 1.8)
Nausea	3.4 (1.5, 6.6)	4.4 (2.9, 6.2)	0.8 (0.3, 1.9)	0.0 (0.0, 0.7)	0.0 (0.0, 0.7)	0.0 (0.0, 1.2)
Asthenia	1.7 (0.5, 4.3)	2.3 (1.3, 3.7)	0.2 (0.0, 0.9)	0.0 (0.0, 0.7)	0.0 (0.0, 0.7)	0.0 (0.0, 1.2)
Malaise	0.0 (0.0, 1.6)	1.5 (0.7, 2.7)	0.0 (0.0, 0.6)	0.0 (0.0, 0.7)	0.0 (0.0, 0.7)	0.0 (0.0, 1.2)
Fever	0.8 (0.1, 3.0)	1.5 (0.7, 2.7)	0.3 (0.0, 1.2)	0.2 (0.0, 1.0)	0.0 (0.0, 0.7)	0.0 (0.0, 1.2)
Pharyngitis	0.4 (0.0, 2.3)	1.4 (0.6, 2.5)	0.3 (0.0, 1.2)	0.2 (0.0, 1.0)	0.2 (0.0, 1.1)	0.0 (0.0, 1.2)
Generalized pain	0.8 (0.1, 3.0)	1.4 (0.6, 2.5)	0.2 (0.0, 0.9)	0.2 (0.0, 1.0)	0.2 (0.0, 1.1)	0.0 (0.0, 1.2)
Arthralgia	0.0 (0.0, 1.6)	0.9 (0.3, 2.0)	1.3 (0.6, 2.5)	0.2 (0.0, 1.0)	0.2 (0.0, 1.1)	0.0 (0.0, 1.2)

a The placebo-treated patients from the preliminary 12-wk segment of this trial[15] are included for comparison purposes.

b Patients who experienced at least one adverse event of the type described during the specified exposure period. The same patient may be counted in multiple categories and/or columns.

c The incidence of adverse events in the placebo group during the randomized treatment phase; 218 of these patients went on to start efalizumab treatment and are included in the subsequent treatment columns.

d Patients who experienced at least one adverse event deemed by the investigator as possibly related to the study drug.

trial: four diagnoses were basal cell carcinoma (BCC) and the remaining nine diagnoses were squamous cell carcinoma (SCC). One patient presented with both BCC and SCC during weeks 49–60 of efalizumab therapy. Another patient presented with three diagnoses of NMSC: SCC diagnosed during weeks 12–24, BCC diagnosed during weeks 25–36 and SCC diagnosed during weeks 37–48 of efalizumab therapy. NMSC is common among psoriasis patients, and the investigator reported the first two of these incidents as unrelated to study drug; however, given the timing and the immunosuppressive nature of efalizumab, the third event was reported as drug related. None of the cases of NMSC reported in the other patients was considered related to the study drug.

One death was reported in this trial, during weeks 36–48 of extended exposure to efalizumab, and was due to severe chronic pulmonary fibrosis with congestive heart failure. There were two deaths in the placebo group of the earlier study (one due to an exacerbation of chronic obstructive pulmonary disease, and the other due to seizure in a patient with a history of epilepsy). The investigators did not consider any of these three deaths to be related to the study treatment.

The incidence of thrombocytopenia remained low and consistent over the 60 weeks of exposure to efalizumab. Seven patients were reported to have an adverse event of thrombocytopenia; of these, four patients had platelet levels that fell below 50 000 platelets/mL. Of these four events, one was not reported as an adverse event, serious or otherwise, two were serious adverse events and one was classified as an adverse event. One of the two serious events of thrombocytopenia was considered severe in intensity. Efalizumab was discontinued for the three patients with adverse (serious or not) events of thrombocytopenia, and the condition resolved without further therapy.

In any 12-week ET segment, the rate of withdrawal because of adverse events ranged from 1.2% to 6.6%. The rate of withdrawal because of psoriasis-related adverse events remained consistent during the course of the study; it was the same (i.e.

Table IV. Selected clinically significant adverse events occurring during any 12-wk period of the placebo-controlled and open-label extension treatment phases[a]

Adverse event[b]	Placebo [n (%)]	Duration of exposure to efalizumab [n (%)]				
	wk 1–12[c] (n = 236)	wk 1–12 (n = 666)	wk 13–24 (n = 622)	wk 25–36 (n = 545)	wk 37–48 (n = 498)	wk 49–60 (n = 309)
Serious adverse event[d]	8 (3.4)	13 (2.0)	22 (3.5)	19 (3.5)	8 (1.6)	7 (2.3)
Death	2 (0.8)	0	0	0	1 (0.2)	0
Diagnosed infection	66 (28.0)	201 (30.2)	177 (28.5)	96 (17.6)	100 (20.1)	64 (20.7)
Psoriasis adverse event	2 (0.8)	14 (2.1)	16 (2.6)	17 (3.1)	15 (3.0)	8 (2.6)
Arthritis adverse event	3 (1.3)	8 (1.2)	13 (2.1)	9 (1.7)	8 (1.6)	7 (2.3)
Malignancy	1[e] (0.4)	0	4[f] (0.6)	4[g] (0.7)	4[h](0.8)	3[i] (1.0)

a The placebo-treated patients from the preliminary 12-wk segment of this trial[15] are included for comparison purposes.

b Patients who experienced at least one clinically significant adverse event of the type described during the specified exposure period. The same patient may be counted in multiple categories and/or columns.

c The incidence of adverse events in the placebo group during the randomized treatment phase; 218 of these patients went on to start efalizumab treatment and are included in the subsequent treatment columns.

d Serious adverse events are defined as events that result in death; life-threatening events; events that result in hospitalization, disability or congenital abnormality; or events that require intervention to prevent permanent impairment or damage to the patient.

e One case of BCC.

f One case of gastrointestinal carcinoma and three cases of SCC.

g One case of breast carcinoma, one case of BCC and two cases of SCC.

h Two cases of SCC and two cases of BCC.

i One case of neuroendocrine carcinoid tumour, one case of BCC and two cases of SCC. One case of SCC was in the patient with BCC.

BCC = basal cell carcinoma; **SCC** = squamous cell carcinoma.

0.3%) during weeks 1–12 of exposure and during weeks 49–60 of exposure.

Discussion

This study extends the safety profile of efalizumab from 12 to 60 weeks of continuous exposure and reinforces data from previously published clinical trials that have demonstrated efalizumab to be well tolerated.[15-20] Moreover, the data contribute significantly to the largest safety database of biological therapies for psoriasis patients treated in psoriasis clinical trials. The safety profile reported here is based on a population of 636 patients who entered the ET phase of the study, and 293 patients who received a total of 60 weeks of efalizumab therapy. The rate of withdrawal within each treatment segment remained comparable with that reported for clinical trials of 12-weeks duration.[16-18]

No new type of common adverse event emerged and no end-organ toxicity resulted during extended exposure to efalizumab. Three deaths that occurred over the course of this study were considered by the investigator to be unrelated to efalizumab therapy. The overall incidence of any adverse events and study drug-related adverse events remained stable or decreased over the course of 60 weeks of continuous efalizumab therapy. The incidence of clinically important adverse events (including the incidence of serious adverse events, diagnosed infections, psoriasis adverse events, arthritis adverse events and malignancy) was comparable in the extended efalizumab treatment period to that observed in the placebo-controlled phase of the trial and remained generally stable with increased exposure to efalizumab. The frequency of immune-mediated thrombocytopenia remained low and <1% throughout each 12-week exposure segment of the trial.

The rate of malignancy remained low and stable at ≤1% for each 12-week exposure throughout the length of the study, and was similar to that reported for the 15- and 27-month data analyses of a 3-year efficacy study.[20,21] The change in malignancy rate from 0% to 1.0% may be accounted for by a bias that can be introduced into an open-label extension of a

randomized, placebo-controlled trial when disorders are screened out before the randomization process.[22] The malignancy rates reported here are in agreement with an analysis of malignancy frequencies performed on multiple pooled clinical trials comprising 2980 efalizumab-treated patients.[23] In addition, increased rates of NMSC have been reported in psoriasis patients, especially in patients treated previously with phototherapy.[24] However, treatment for longer periods in a large number of patients is necessary to determine whether or not efalizumab has an effect on cancer rates; a registry has been initiated to examine the incidence of malignancy in long-term efalizumab-treated patients.

The results of this safety analysis are similar to those found for short-term efalizumab trials[15-19] and to a long-term efficacy trial,[20,21,25] supporting the safety and tolerability profile for long-term administration of efalizumab.

Conclusions

An extended efalizumab trial with exposure of patients for up to 60 weeks (15 months) has demonstrated that efalizumab was well tolerated and that the safety profile remained similar to that observed in short-term therapy trials of 12 and 24 weeks as well as long-term trials through 36 months. The results reported here reinforce and extend the safety profile of efalizumab.

Chronic autoimmune diseases such as psoriasis may require long-term treatment, and further study of the long-term efficacy and safety of efalizumab is warranted. Efficacy and safety results from a 3-year study of efalizumab in psoriasis patients have recently been reported[25] and extend the safety results observed here. In the US, the RESPONSE study,[26] and in Canada the RESTORE study,[27] are 5- and 4-year, respectively, open-label, multicentre, observational studies enrolling efalizumab-treated patients and are designed to assess the long-term safety of efalizumab for the treatment of chronic moderate to severe plaque psoriasis. The data reported herein provide insight to the safety profile of efalizumab for up to 15 months of treatment and the longer-term safety data from the 3-year study and the data expected from the two observational studies will considerably expand the experience with this molecule.

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