National PBM Drug Monograph

Efalizumab (RAPTIVA™)

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VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Mechanism of Action: Efalizumab is an immunosuppressive, recombinant humanized anti-CD11a monoclonal antibody (mAb) that blocks the activation, adhesion, and trafficking of T-cells.

FDA–Approved Indication: Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The drug is also being evaluated for psoriatic and rheumatoid arthritis.

Safety: Efalizumab was associated with a relatively low rate of serious adverse events, with no observed increased frequency of malignancies and serious infections over placebo, but long-term data is lacking.

- The rate of non-melanoma skin cancer was higher than expected rates based on non-randomized external cohorts.
- Reversible, possibly immune-mediated thrombocytopenia occurred infrequently but unpredictably.
- Cases of psoriasis worsening or rebound, some serious and requiring hospitalization, occurred predominantly after discontinuation of treatment. It is recommended that patients should be transitioned to alternative antipsoriatic treatment as necessary. The optimal method of managing and preventing psoriatic flares upon discontinuation of efalizumab has not been determined.
- The uncertain long-term risks of thrombocytopenia, malignancies, infections, and autoimmune diseases and the lack of data from study patients similar to the veteran population must be weighed against the potential advantages of the drug.

Efficacy: Efalizumab (0.7 mg/kg initially then 1 mg/kg subcutaneously every week) is moderately efficacious as continuous treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Efalizumab does not induce long-term remission and, unlike other antipsoriatic treatments, appears to lose efficacy upon retreatment of patients in relapse.

Comparison with Other Systemic Treatments for Plaque Psoriasis: Studies directly comparing efalizumab with other systemic antipsoriatic medications are required to better delineate its place in therapy and relative safety and cost-effectiveness. Further studies are needed to determine the safety and efficacy of efalizumab in other types of psoriasis and as part of combination, rotational, or sequential systemic therapy. Potential advantages of efalizumab over other systemic antipsoriatic agents are possibility of self-administered injections, lack of lymphopenia or decreased CD4+ cell counts, lack of a need for weekly monitoring of blood counts, and lack of renal, hepatic, or pulmonary toxicity.

Recommendations: Efalizumab should be nonformulary at both national and VISN levels with criteria for use and restricted to clinicians experienced in the treatment of moderate to severe psoriasis. It should be used as systemic monotherapy in patients with severe plaque psoriasis who have had an inadequate response, contraindication, intolerance, or hypersensitivity to conventional treatment (topical agents, ultraviolet therapy, acitretin, and methotrexate).

Introduction

Psoriasis has gained acceptance as an autoimmune disorder mediated by T-cells. Patients with moderate to severe psoriasis are often inadequately controlled with topical agents and require ultraviolet or systemic therapy. The more useful systemic therapies are often immunosuppressives, such as methoxsalen (psoralen) with ultraviolet A radiation (PUVA), ultraviolet B radiation (UVB), glucocorticoids, methotrexate, and cyclosporin.

The first biologic agent approved by the Food and Drug Administration (FDA) for moderate to severe plaque psoriasis, alefacept (Amevive®), is an immunosuppressive dimeric fusion protein. Two other immunosuppressive biologic agents, infliximab[1,2] and etanercept[3,4], are cytokine inhibitory tumor necrosis factor–α (TNF-α) antagonists that have also shown efficacy in moderate to severe plaque psoriasis. Infliximab is approved in the U.S. for the treatment of rheumatoid arthritis and Crohn's disease, and etanercept is approved for the treatment of rheumatoid arthritis and psoriatic arthritis, but neither agent has been approved yet for treatment of plaque psoriasis.

Currently approved therapies for psoriasis have disadvantages that limit their long-term use. Ultraviolet irradiation is inconvenient and is associated with a risk of cancer. Methotrexate may cause bone marrow depression, liver toxicity, and pulmonary toxicity. Cyclosporin may impair renal function. Alefacept may cause lymphopenia, requires weekly monitoring of CD4+ T-cell counts, and must be administered intravenously or intramuscularly under physician supervision.

Efalizumab (formerly MHM24, hu1124, Xanelim) is the second biologic agent to be approved for moderate to severe plaque psoriasis. The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating efalizumab for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Mechanism of Action

Efalizumab is an immunosuppressive, recombinant humanized IgG1 anti-CD11a monoclonal antibody (mAb) that blocks the activation, adhesion, and trafficking of T-cells. It binds to, saturates, and reduces the expression of CD11a, the α subunit of leukocyte function antigen-1 (LFA-1), the predominant integrin expressed on T-cells. Efalizumab blocks the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1) and thereby inhibits the adhesion of leukocytes to other cell types.

CD11a is also expressed on the surface of B lymphocytes, monocytes, neutrophils, natural killer cells, and other leukocytes. Therefore, the potential exists for efalizumab to affect the activation, adhesion, migration, and numbers of cells other than T lymphocytes.

Pharmacokinetics

There is limited pharmacokinetic data on subcutaneously administered efalizumab (Table 1).

Table 1 Pharmacokinetics of efalizumab[†]

Parameter	N	Mean	Range
Bioavailability (s.c.)	—	50%	—
Time to steady state	26	4 wk	—
Time to eliminate[‡]	17	25 d	13–35 d
Clearance	25	24 ml/kg/d	5–76 ml/kg/d

Source: RAPTIVA (efalizumab) package insert[5]

[†] Following efalizumab 0.7 mg/kg s.c. then 1 mg/kg/wk s.c. for 11 weeks in patients with moderate to severe plaque psoriasis.

[‡] After last steady-state dose

Clearance is affected by body weight (N = 1088; no further details available). At a dose of 1 mg/kg/wk subcutaneously, exposure to efalizumab is similar across body weight quartiles. Clearance is not affected by gender or race.

The pharmacokinetic characteristics of the drug have not been studied in children and adolescents (age less than 18 years) and patients with renal or hepatic impairment.

FDA Approved Indication

Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Off-label Uses

There is currently one small double-blind randomized controlled trial (DB RCT) that suggests efalizumab may reduce the late asthmatic response in patients with mild *allergic asthma*.[6]

The drug is being evaluated in a phase II trial for *rheumatoid arthritis*. A phase I trial is planned for *psoriatic arthritis*. A phase I/II trial showed that combination immunosuppressive therapy with efalizumab was potentially effective in *renal transplantation*; however, clinical development may be limited because high doses of the drug may cause post-transplant lymphoproliferative disease.[7]

Current VA National Formulary Status

Nonformulary, new molecular entity.

Dosage and Administration

Efalizumab therapy is initiated with a low conditioning (tolerization) dose to reduce the risk of dose-dependent adverse events (see *Adverse Events*). Subsequently, efalizumab is given as fixed subcutaneous doses based on total body weight. The weekly dose of 1 mg/kg produces maximal saturation and down modulation of CD11a.[8] Increasing the weekly dose to 2 mg/kg produces no apparent additional benefit.[9,10]

Conditioning dose	0.7 mg/kg s.c. x 1 dose
Maintenance dose	1 mg/kg s.c. weekly
Maximum single dose	200 mg
Discontinuation	Monitor patient closely for worsening of psoriasis and institute alternative antipsoriatic treatment as necessary.

In a meeting of the Food and Drug Administration (FDA) Dermatologic and Ophthalmic Drugs Advisory Committee to discuss the biologics licensing application of efalizumab, serious adverse events of psoriasis that were observed in clinical trials were attributed to psoriasis worsening or rebounding (worsening past baseline)[11] (also see *Adverse Events).* Preliminary, anecdotal experience from an unpublished, ongoing transition study suggest that immediately transitioning to alternative antipsoriatic therapy or overlapping efalizumab with the replacement therapy for about two weeks may prevent flares.[11] Efalizumab should not be abruptly discontinued without close monitoring or drug transitioning, even in patients who are worsening or not responding on treatment. Appropriate follow-on therapies have not been evaluated in clinical trials. The safety of using efalizumab concomitantly with antipsoriatic medications other than some topical medications has not been evaluated.

Efalizumab is intended for use under the guidance and supervision of a physician. If determined to be appropriate, self-injection of the drug is possible after the patient receives proper training in reconstitution and administration techniques.

Reconstitution

Efalizumab comes in cartons containing four trays. Each tray contains one single-use vial of 125 mg of efalizumab as a sterile lyophilized powder without antibacterial preservatives, one single-use prefilled syringe containing diluent (1.3 ml sterile water for injection, two 25-gauge x 5/8 inch needles, two alcohol prep pads, a package insert, and a patient information insert.

Efalizumab should be reconstituted to a final concentration of 100 mg/ml immediately before use by injecting the sterile water diluent into the vial of drug. The vial must be GENTLY swirled to dissolve the powder (usually less than 5 minutes). The vial should not be shaken, as this will cause foaming. The reconstituted solution should be clear to pale yellow and free of particulates. If the solution is discolored or contains particulates, it should not be used.

Each vial should be used only once. No other diluents should be used to reconstitute efalizumab. No other medications should be added to the solution of efalizumab.

Administration

The needle on the syringe should be replaced with a new needle prior to drawing up the required dose from the vial of efalizumab solution. Efalizumab should be administered subcutaneously, rotating injection sites. Sites for injection include the thigh, abdomen, buttocks, or upper arm.

Unused efalizumab solution should be discarded.

Storage

Efalizumab lyophilized powder must be refrigerated at 2–8°C (36–46°F). The drug should be stored in its original carton and protected from light.

If reconstituted efalizumab is not used immediately, it may be stored at room temperature and used within 8 hours.

Dosing in Special Populations

No clinical studies have been conducted in children and adolescents (age less than 18 years) and patients with renal or hepatic impairment.

Adverse Events (Safety Data)

The following information was obtained primarily from a transcript of a meeting between Genentech and the FDA Dermatologic and Ophthalmic Drugs Advisory Committee. Both the manufacturer and the FDA discussed their analyses of pooled data from four phase III DB RCTs and 3 open-label studies.[11] The results of only two of the DB RCTs have been published[9,12] (see *Published Double-Blind Randomized Trials Evaluating Efalizumab in Psoriasis*). Information was also obtained from the package insert.[5]

The safety data is based on a total of 2762 patients with moderate to severe psoriasis who were treated with efalizumab during clinical trials, including doses higher than the recommended weekly dose of 1 mg/kg.[5,13,14] A total of 904 patients have been treated with efalizumab for 6 months or longer and 218 patients have been treated with efalizumab for one year or longer. The overall drug exposure translates into 1790 patient-years of experience in efalizumab-treated patients.

Summary of Safety Data

- Efalizumab was associated with a relatively low rate of serious adverse events, with no observed increased frequency of malignancies and serious infections over placebo.
- The rate of non-melanoma skin cancer was higher than expected rates based on non-randomized external cohorts, suggesting that efalizumab may be associated with an increased risk of this type of cancer. No definitive conclusions can be made, however, because of the possibility of ascertainment bias.
- Reversible, possibly immune-mediated thrombocytopenia occurred infrequently but unpredictably, with an onset that varied from 8 to 72 weeks after start of treatment.
- Psoriasis adverse events, some serious and requiring hospitalization, occurred predominantly after discontinuation of treatment. These events may be manageable with immediate institution of alternate antipsoriatic therapy or overlapping therapies when discontinuing efalizumab. The optimal method of managing and preventing psoriatic flares upon discontinuation of efalizumab has not been determined.
- Efalizumab does not decrease, but rather increases, lymphocyte counts.
- There was no evidence of renal, hepatic, or pulmonary toxicity.
- Mild flu-like symptoms were the most common adverse events, often occurring within 48 hours of the initial dose.
- There is limited safety data on doses greater than 2 mg/kg, the long-term continuous use of efalizumab beyond 1 year, or possible latent complications after discontinuation of its use. The long-term risks of infections, autoimmune diseases, lymphoma, and skin cancer, have not been adequately assessed.

– The use of efalizumab in combination with other systemic drug or ultraviolet therapy has not been evaluated in clinical trials, and concurrent use with other immunosuppressives is not recommended. There is limited, unpublished experience with adding other systemic treatments immediately after discontinuation of efalizumab.

Deaths and Other Serious Adverse Events

There were no deaths in the placebo-controlled trial periods, 2 deaths during treatment after the first 12 weeks, and 5 deaths after treatment. No deaths were causally linked to efalizumab in clinical trials.[11]

The overall rate of serious adverse events occurring on efalizumab during the placebo-controlled periods from four phase III major efficacy trials was low (2.0% to 2.9%) and similar to that of placebo (1.7%) (Table 2).

Table 2 Serious adverse events (SAEs) during placebo-controlled periods of phase III clinical trials (pooled data)

		Efalizumab	
Description[†]	**Placebo (N = 715)**	**1 mg/kg (N = 1213)**	**2 mg/kg (N = 407)**
Cellulitis	0.0%	<0.1%	0.5%
Kidney calculus	0.0%	0.2%	0.2%
Accidental injury	0.0%	<0.1%	0.2%
Atrial fibrillation	0.0%	<0.1%	0.2%
Coronary artery disease	0.0%	<0.1%	0.2%
Gastroenteritis	0.1%	<0.1%	0.2%
Pneumonia	0.0%	0.2%	0.0%
Skin carcinoma	0.1%	0.2%	0.0%
Depression	0.3%	<0.1%	0.0%
Patients with at least one SAE	**1.7%**	**2.0%**	**2.9%**

Source: *RAPTIVA (efalizumab) Safety*, Genentech presentation to FDA Dermatologic and Ophthalmic Drugs Advisory Committee[11,13]

[†] Serious adverse events observed in at least two patients during placebo-controlled periods of phase III clinical trials

There was no clear dose-dependent effect or increase in serious adverse events over time (up to 60 weeks).

Common Adverse Events

Acute Adverse Events (First-dose Reactions)

To reduce the risk of acute adverse events (first-dose reactions) in phase III clinical trials, efalizumab was administered subcutaneously starting with a low initial conditioning or tolerization dose (0.7 mg/kg) followed by higher weekly doses (1 or 2 mg/kg). After the initial dose (0.7 mg/kg) of this regimen, acute adverse events (prospectively defined as headache, nausea, vomiting, fever, chills, or myalgia occurring within 48 hours of efalizumab injection) were observed in more efalizumab patients (28% to 29%) than placebo patients (15%).[13] With the third and subsequent doses (efalizumab 1 or 2 mg/kg), however, the rates of acute adverse events were lower (about 1% to 5%) and similar between active treatment and placebo groups.

The acute adverse events were generally short-lived (median duration, 1 to 2 days), were relieved with acetaminophen or nonsteroidal antiinflammatory drugs, and led to discontinuation of efalizumab in less than 1% of patients.

Other Common Adverse Events

Table 3 shows the most common adverse events that occurred at a frequency that was 2% or greater in the efalizumab (1 mg/kg weekly) group than the placebo group in the placebo-controlled trial periods.

Table 3 Adverse events occurring at a ≥ 2% higher rate on efalizumab 1 mg/kg/wk than placebo (pooled data, placebo-controlled trial periods)

Description	Placebo (N = 715)	Efalizumab (N = 1213)
Headache	159 (22%)	391 (32%)
Infection	188 (26%)	350 (29%)
Chills	32 (4%)	154 (13%)
Nausea	51 (7%)	128 (11%)
Pain	38 (5%)	122 (10%)
Myalgia	35 (5%)	102 (8%)
Flu Syndrome	29 (4%)	83 (7%)
Fever	24 (3%)	80 (7%)
Back Pain	14 (2%)	50 (4%)
Acne	4 (1%)	45 (4%)

Source: RAPTIVA (efalizumab) Package Insert[5]

Specific Adverse Events

Malignancies

The data are limited because the duration of the studies to date are insufficient to detect cancer due to the latency following onset of treatment. Only 218 patients have been treated longer than 1 year. Analysis of the pooled safety data showed that the incidence of all malignancies was low and similar between efalizumab (1.68 per 100 patient-years, 30/1782 patient-years) and placebo groups (1.62 per 100 patient-years, 3/185 patient-years).[13] The rates for each type of malignancy were similar between treatment groups: non-melanoma skin cancer (1.12 per 100 patient-years on efalizumab versus 1.08 on placebo), melanoma (0.06 versus 0.00), solid tumor (0.45 versus 0.54), and lymphoma (0.06 versus 0.00). The number of cases of non-melanoma skin cancer on efalizumab (20, 95% CI: 12 to 31) was higher than the expected rate based on external cohorts (Saskatchewan Health: 7, 4 to 11 and United Health Care: 7, 4 to 11).[11,14] No post hoc subanalysis was performed on the data from patients with more than one year of exposure to efalizumab, and no data was reported on squamous cell carcinoma of the skin.[11]

It is important to note that in a separate safety database from trials evaluating efalizumab for renal transplantation, 3 of 38 renal transplant patients developed post-transplant lymphoproliferative disorder.[11] All of the cases occurred on efalizumab 2 mg/kg weekly for 12 weeks in patients on triple immunosuppressive therapy. One case resulted in death considered by the investigator to be related to efalizumab.

Serious Infections

Serious infections requiring hospitalization included cellulitis, pneumonia, abscess, sepsis, bronchitis, gastroenteritis, aseptic meningitis, Legionnaire's disease, and vertebral osteomyelitis.[5] The incidence of serious infections requiring hospitalization tended to be higher on efalizumab than on placebo; however, the rate on placebo was based on only 2 occurrences in 169 patient-years (Table 4).

Table 4 Serious infections requiring hospitalization (pooled data)

	Placebo	Efalizumab	External psoriasis cohort†
Rate (events / pt-yrs)	2/169	27/1680	73/4056
Incidence (per 100 pt-yrs)	1.2	1.6	1.80
95% CI	0.1–4.3	1.1–2.3	1.41–2.27

Sources: *RAPTIVA (efalizumab) Safety*, Genentech presentation to FDA Dermatologic and Ophthalmic Drugs Advisory Committee[13]; *Biologic License Application STN BL 125075/0: Efalizumab for the Treatment of Chronic Plaque Psoriasis*, FDA clinical reviewer's presentation to the same committee[14]

† Saskatchewan Health claim database

The incidence of serious infections requiring hospitalization did not seem to be higher than the expected background rate based on an external epidemiological cohort. In most cases, efalizumab could be continued or held for 1 to 2 doses during an infection. Other than one case of Legionnaire's disease, opportunistic infections such as tuberculosis and *pneumocystis carinii* pneumonia were not seen.

Thrombocytopenia

In the pooled safety data from clinical trials (2762 efalizumab patients), there were 8 cases (0.3%) of reversible thrombocytopenia reported as a serious adverse event (because of hospitalization, 5 cases) or with a platelet count less than 52,000.[5,11] Two patients had nadir platelet counts of less than 10,000. Three patients developed bleeding complications. The onset of thrombocytopenia varied from 8 to 72 weeks after the first dose of efalizumab.

All cases of thrombocytopenia occurred on efalizumab therapy; no cases were reported on placebo.[5,11] Six cases seemed to be consistent with possible drug-induced immune thrombocytopenia; however, there were confounding factors in all cases, including Grave's disease (n = 2), viral syndrome (n = 3), other drugs (n = 1), prostate cancer (n = 1) and pre-existing idiopathic thrombocytopenic purpura (n = 1). Causality between efalizumab and thrombocytopenia remains to be established.

Worsening, rebound, and variants of psoriasis

Overall, during the placebo-controlled periods of the phase III clinical trials, about 3.2% of efalizumab (N = 1620) and 1.4% of placebo patients (N = 715) reported a psoriasis adverse event, which most commonly consisted of mild to moderate guttate psoriasis.[13] These events led to discontinuation of efalizumab in less than 0.6% of the patients. Of 143 patients who completed a washout period following abrupt discontinuation of efalizumab, 18% experienced rebound (more than 25 percent above their baseline psoriasis severity) at 12 weeks.[11] This rate of rebound was similar to the rate of 17.8% seen after 12 weeks of placebo during the initial controlled trial period. However, the development of psoriasis variants including guttate, erythrodermic, and pustular psoriasis (types of psoriasis that had been excluded from the trials) was concerning, with all erythrodermic and generalized pustular psoriasis cases being seen only on efalizumab and not on placebo.[11] In addition, of 2762 efalizumab-treated patients, 19 (0.7%) developed serious psoriasis adverse events that resulted in hospitalization of 17 patients.[5,13] Most (14, 74%) of the cases occurred after discontinuation of efalizumab and 5 (26%) occurred during efalizumab treatment. (Worsening of psoriasis may have been related to the design of initial trial protocols, in which efalizumab was discontinued without tapering or transitioning to other systemic antipsoriatic drug therapy, and the use of antipsoriatic medication was restricted until there was loss of more than 50% of the improvement gained on therapy.)

Serious Arthritis

There were 15 patients (0.6%) who developed arthritis as a serious adverse event (usually requiring hospitalization). These cases included psoriatic as well as inflammatory arthritis. One

case was associated with other findings of inflammation, fever, cellulitis, and a positive antinuclear antibody titer. All of these events occurred after the first 12-weeks of placebo-controlled trials.[11,15]

Other inflammatory conditions
Other potentially autoimmune-mediated inflammatory conditions developed rarely during reuse of efalizumab, including interstitial pneumonitis (2 patients), a serum sickness-like reaction (1 patient), transverse myelitis (1 patient), and idiopathic hepatitis (1 patient).[11]

Tolerability

Efalizumab was generally well tolerated. Adverse events that led to discontinuation included first-dose reactions (< 1%), infection (< 1%), psoriasis (0.6%), pain (0.4%), arthritis (0.4%), and arthralgia (0.3%).

Laboratory changes

Efalizumab increases white blood cell, lymphocyte, and eosinophil counts (Table 5). This effect is consistent with the finding that efalizumab decreases leukocyte adhesion to blood vessel walls and decreases trafficking from the vascular compartment to tissues.

Table 5 Effects on White Blood Cells

Blood cell type	Relative (%) Change	N (%) Above Normal[†]
White blood cells	34%	213/676 (32%)
Lymphocytes	100%	324/701 (46%)
Eosinophils	29%	35/675 (5%)

Source: RAPTIVA (efalizumab) Package Insert[5]

[†] Results at Day 56 of efalizumab 1 mg/kg/wk s.c.

After discontinuation of efalizumab, high lymphocyte counts took about 8 weeks to normalize among patients with abnormal counts. Effects on platelet counts are discussed under *Specific Adverse Events*, *Thrombocytopenia.*

After subcutaneous administration of efalizumab (0.7 mg/kg), IL-6 increased 2-fold as compared with baseline values (10 pg/ml versus 5 pg/ml), whereas TNF-α was not detectable. C-reactive protein and fibrinogen increased by 67% and 15%, respectively, over baseline. The clinical relevance of these changes is unclear.

Predominantly low-titer antibodies to efalizumab developed in 67 (6.3%) of 1063 patients evaluated for antibodies after treatment ended. The long-term immunogenicity of efalizumab is unknown.

Contraindications

Hypersensitivity to efalizumab or any of its components.

Warnings

Serious Infections

Efalizumab should not be administered to patients with clinically important infections. Use caution in patients with a chronic infection or history of recurrent infections, as efalizumab may reactivate latent, chronic infections, such as tuberculosis. Patients who develop new infections during efalizumab therapy should be monitored. In high risk patients, consider purified protein derivative (PPD) testing and/or chest X-rays before starting efalizumab.

Malignancies

Use caution when considering the use of efalizumab in patients with high risk for, or a history of, malignancy. Discontinue efalizumab if a patient develops a malignancy.

Thrombocytopenia

Physicians should closely monitor patients for signs and symptoms of thrombocytopenia, and check platelet counts periodically (see *Precautions*, *Thrombocytopenia*).

Psoriasis Worsening and Variants

Patients, including those not responding to efalizumab, should be closely monitored following discontinuation of efalizumab, and appropriate alternative antipsoriatic treatment instituted as necessary. When efalizumab is discontinued, transitioning to alternative antipsoriatic medications has been suggested to prevent exacerbation (rebound) of psoriasis[11] (also see *Dosage and Administration*). There is no clinical evidence available to guide the selection of antipsoriatic agents that may be safely and effectively used immediately upon discontinuation of efalizumab. The use of Eucerin cream, tar or salicylic acid preparations for scalp psoriasis, and limited application of low-potency glucocorticoids were allowed during clinical trials. The use of other immunosuppressive agents is not recommended during efalizumab therapy.

Precautions

Immunosuppression

The use of efalizumab in combination with other immunosuppressive agents or phototherapy has not been evaluated for safety and efficacy, and is not recommended because of the potential for increased risk of infections and malignancies.

Immunizations

The safety and efficacy of vaccinations during efalizumab therapy have not been evaluated. Indirect evidence from a small clinical study suggests that the recommended dose (1 mg/kg subcutaneously) may decrease the secondary immune response.[5] Acellular, live, and live-attenuated vaccines should not be administered during efalizumab therapy. Clinicians should consider deferring active immunization until after discontinuation of efalizumab. In pharmacodynamic studies, CD11a expression returned to a mean of 74% of baseline at 5 weeks and remained at comparable levels at 8 and 13 weeks, and free CD11a bindings sites returned to a mean of 86% of baseline at 8 weeks and remained at comparable levels at 13 weeks.[5] No further assessments of CD11a expression and free CD11a binding sites were made after 13 weeks. The degree of antibody response after active immunization in humans has not been evaluated after discontinuation of efalizumab; therefore, the optimal interval to delay immunization after stopping efalizumab has not been determined.

First-dose Reactions

A conditioning dose of 0.7 mg/kg subcutaneously is recommended when starting efalizumab to reduce the risk of dose-dependent, acute flu-like symptoms that tend to occur within 48 hours of the first or second weekly dose. (See *Dosage and Administration*.)

Thrombocytopenia

Platelet counts are recommended when initiating therapy (e.g., monthly) and periodically thereafter (e.g., every 3 months). Serious thrombocytopenia has been observed during efalizumab therapy (see *Specific Adverse Events*, page 7).

Pregnancy

Category C. Risk of fetal harm, including maldevelopment of the immune system, and effects on reproductive capacity when efalizumab is administered to pregnant women are unknown. Administer to pregnant women only if clearly needed. Health care providers are encouraged to enroll patients who become pregnant during efalizumab treatment or within 6 weeks of discontinuing efalizumab into the RAPTIVA Pregnancy Registry.

Nursing Mothers

It is not known whether efalizumab is excreted in human milk. Animal data suggest the potential for nursing infants to have reduced ability to mount an antibody response.[5] Consider options to either discontinue nursing during efalizumab therapy or discontinue the drug.

Geriatric Use

In controlled trials, 128 patients 65 years or older and 2 patients 75 years or older were treated with efalizumab (N = 1620). No apparent differences in safety or efficacy were observed between older and younger patients; however, the number of elderly patients may have been insufficient to detect true differences. Use caution when using efalizumab in elderly patients because of their increased risk for infections.

Patient Information and Training

Patients should be informed of the need to check platelet counts during therapy. They should be advised to inform their health care provider of any signs or symptoms of thrombocytopenia, such as unusual bleeding, bruising, or petechiae.

Patients should also be informed that efalizumab is an immunosuppressant and may increase their risks of infections and malignancies. Patients should be advised that they should promptly inform their prescribing physician if they develop any new signs or are given a new diagnosis of infection or malignancy during efalizumab therapy.

Patients should be warned that abrupt discontinuation of efalizumab may result in worsening or rebound of psoriasis. Treatment with efalizumab should be discontinued under medical supervision.

Women who become pregnant during efalizumab therapy or within 6 weeks of discontinuing treatment should be advised to inform their prescribing physician and consider enrolling in the RAPTIVA Pregnancy Registry.

Patients or caregivers who will be administering efalizumab should be instructed on proper preparation and administration of doses and applicable state or local laws regarding disposal of needles and syringes. Patients should be advised not to reuse needles and syringes.

Drug Interactions

Drug interaction studies have not been performed with efalizumab. Other immunosuppressants and acellular, live, and live-attenuated vaccines should not be administered during efalizumab therapy.

Major Efficacy Measures

Psoriasis Area and Severity Index (PASI) 75 and 50

The PASI is a composite score ranging from 0 to 72 that is based on the physician's assessment of the extent of affected skin surface area and the severity of erythema, desquamation, and plaque induration. The higher scores indicate more severe disease and a reduction in the score indicates improvement. The standard used by the FDA to evaluate antipsoriatic treatments is the PASI-75,

which is improvement of at least 75 percent in the PASI. Clinically meaningful improvement, including "excellent" responses, however, can occur with less than 75 percent improvement. Many clinicians and patients with severe psoriasis would consider a PAS1-50, which is improvement of at least 50 percent in the PASI, to be an excellent response. Therefore, PASI-50 is also reported as a secondary outcome measure. An important limitation of the PASI score is that very different objective and subjective assessments of disease status can be represented by comparable PASI scores.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item questionnaire that was developed as a practical measure of the impact of skin disease (psoriasis) on the patient's quality of life over the previous 7 days. The 10 questions evaluate specific problems and each question has four possible responses: "not at all," "a little," "a lot," or "very much," with scores of 0, 1, 2, and 3, respectively. The DLQI represents the sum of the scores, ranging from 0 to 30 points. The DLQI score has a weak association with extent of clinical improvement, and was not designed to measure treatment efficacy for research purposes. The problems evaluated in the DLQI are weighted equally and may not reflect differences in the severities of the problems. The DLQI is subject to language translational problems, and the scale may be interpreted differently by different cultures (e.g., "a lot" and "very much" may be identified as being very different in the United Kingdom but similar in the United States).[16]

Static PGA (sPGA) or Overall Lesion Severity (OLS)

The sPGA or OLS is a static global assessment with a 6-category scale ranging from "very severe" to "clear" and indicates the physician's overall assessment of the psoriasis severity focusing on plaque, scaling, and erythema.

Physician's Global Assessment (PGA)

The PGA is a dynamic evaluation of the global response to therapy compared with baseline status on a 7-point scale ranging from worse to cleared. Physicians assess all clinical signs and symptoms available, including subjective information from the patient and photographs. The proportion of patients obtaining "clear or almost clear/excellent" is probably the best composite metric of short-term efficacy (assuming other treatment-dependent variables that may affect the patient's life do not worsen, such as inconvenience, cost, or adverse effects).

Summary of Efficacy

- Subcutaneously administered efalizumab has demonstrated moderate efficacy in terms of PASI-75 response rates (difference between efalizumab and placebo: 17% to 37%) and quality of life measures when the drug is administered as continuous systemic monotherapy (in conjunction with some topical therapies) for chronic moderate to severe plaque psoriasis.
- The median onset of significant improvement in PASI scores is about 4 weeks.
- After discontinuation in responders, efalizumab maintains a relatively short remission period of about 2 months, consistent with its reversible effects on CD11a expression. *It should not be considered a disease-remitting agent.*
- The drug is best suited for continuous rather than intermittent treatment, because of the following:
    - The majority (67%) of PASI-75 responders will relapse when efalizumab is discontinued.
    - Efficacy is maintained with long-term treatment; however, there is data from only 219 patients who were treated for one year or longer.

  - Retreatment of previous PASI-75 responders who relapse after discontinuation of efalizumab appears to be less efficacious (31% achieved PASI-75 response) than first treatment. This loss of efficacy upon retreatment of patients in relapse seems to be unique to efalizumab among the available antipsoriatic treatments. It also implies that efalizumab may not be as efficacious for psoriasis in flare as it is for stable plaque psoriasis.
  - Many partial responders (PASI-50) at 12 weeks achieved full response (PASI-75) at 24 weeks.
  - PASI-75 responders to efalizumab in the first 12 weeks of treatment seemed to be more likely to obtain a PASI-75 response with continued therapy than patients with limited (PASI-50) response. Patients with less than 50% improvement at week 12 were less likely to achieve a PASI-75 response with an additional 12 weeks of therapy at a higher dose.
- Head-to-head comparisons between efalizumab and other antipsoriatic treatments are lacking.
- The efficacy of efalizumab in patients with other than plaque-type psoriasis (e.g., pustular, erythrodermic, or guttate psoriasis), unstable psoriasis, or active psoriatic flare has not been studied.
- The efficacy of efalizumab as part of combination, rotational, or sequential systemic antipsoriatic treatment regimens has not been studied.

Clinical Trials

Four phase III placebo-controlled, double-blind, randomized major efficacy trials and three phase III open-label trials have been completed or are still ongoing as part of the agreement for the FDA biologics licensing application. Two of the double-blind studies (2390 and 2600) evaluated the approved product manufactured by Genentech. Two earlier studies (2058 and 2059) evaluated the Xoma product or both Xoma and Genentech products. The Xoma product differed in pharmacokinetics from the Genentech product but was not different in terms of safety or efficacy.[14]

The results of only two of these trials (2059 and 2390)[9,12] have been published and are tabulated in this report (see *Published Double-Blind Randomized Trials Evaluating Efalizumab in Psoriasis*). Published open-label phase I trials[17,18] and a phase II DB RCT evaluating intravenous efalizumab,[19] which is not approved, are not included in this report.

Evidence supporting continuous treatment with efalizumab is based on data from 500 patients for 36 weeks, 219 patients continuously treated for at least 48 weeks, and 153 patients for at least 84 weeks. One study will include treatment out to 3 years.

Summary of Findings from Selected Phase III Trials

Table 6 summarizes major efficacy findings from selected phase III trials which were discussed between Genentech and the FDA Dermatologic and Ophthalmic Drugs Advisory Committee.[10,11,14]

Table 6 Major Efficacy Findings from Selected Phase III Trials

<table>
<tr><th>Study Number</th><th>Important Findings</th></tr>
<tr><td>2059
2390
(Published)
2058
2600
(Unpublished)</td><td>The four placebo-controlled DB RCTs were similar in patient populations, treatment regimens, and primary end points. The treatment effect (difference between efalizumab 1 mg/kg s.c. weekly and placebo) was reproducible across the four trials. The absolute difference between treatments in the proportion of patients achieving PASI-75 at week 12 ranged from 17% to 37% among the four studies. Secondary efficacy results supported the primary efficacy analyses.
<table>
<tr><th rowspan="2">Study</th><th colspan="2">Treatment difference in PASI-75 Responders (Efaluzimab – Placebo)</th></tr>
<tr><th>% of pts</th><th>95% CI</th></tr>
<tr><td>2059</td><td>17%</td><td>9% to 27%</td></tr>
<tr><td>2390</td><td>22%</td><td>16% to 29%</td></tr>
<tr><td>2058</td><td>37%</td><td>28% to 46%</td></tr>
<tr><td>2600</td><td>21%</td><td>15% to 27%</td></tr>
</table></td></tr>
<tr><td>2058
(Unpublished)</td><td>Retreatment with efalizumab for 12 weeks is efficacious in patients with a previous PASI-75 response who were relapsing after discontinuation of efalizumab; however, the response rate to retreatment was much lower in previous PASI-75 responders. Relapse was defined as loss of 50% of the improvement that had been gained at week 12. PASI-75 was achieved upon retreatment in 31% of 55 efalizumab-treated relapsing patients who were previous PASI-75 responders (34% of 32 patients in the 1 mg/kg group and 25% of 23 patients in the 2 mg/kg group) versus 0% of 27 placebo-treated relapsing patients ($p < 0.001$).[15]

About 50% of the patients who had a previous PASI-75 response (N = 107) had relapsed by 9 weeks following discontinuation of efalizumab.</td></tr>
<tr><td>2243
(Unpublished)</td><td>PASI-75 at 48 weeks was 45%. This result confirmed the PASI-75 response rate of 44% at 24 weeks from study 2391 and suggested that the response at 24 weeks could be maintained out to 48 weeks.</td></tr>
</table>

Published Double-Blind Randomized Trials Evaluating Efalizumab in Psoriasis

Citation

Gordon KB, Papp KA, Hamilton TK et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 2003;290(23):3073-80

Study Goals

To assess the efficacy and safety of efalizumab in patients with plaque psoriasis.

Methods

Study Design

Phase III multicenter (30 centers in U.S. and Canada), placebo-controlled, parallel-group, double-blind, randomized trial (pivotal trial, study 2390). Allocation concealed. Sample size and power calculated.

Patients were randomized in a 2:1 ratio to efalizumab 0.7 mg/kg conditioning dose x 1 then 1 mg/kg/wk s.c. x 11 wk or placebo (total 12 wk)

After the 12 wk of placebo-controlled treatment, all patients were enrolled in a separate long-term open-label extension study (2391).

Data Analysis

ITT population (all randomized patients) for primary and secondary efficacy analyses. As-treated population for safety analyses (excluded 1 patient who was randomized but discontinued before receiving any study drug). Patients who discontinued the study early or whose week 12 PASI score was missing were classified as nonresponders.

Primary efficacy outcome: Proportion of patients with at least 75% improvement in PASI (PASI-75) at week 12 relative to baseline; comparison of treatments was analyzed by Fisher's exact test for binomial outcome.

Secondary efficacy variables: OLS (sPGA), PGA, DLQI, Itching Visual Analog Scale (VAS), and Psoriasis Symptom Assessment (PSA) frequency and severity subscales; Hochberg-Bonferroni multiple-comparisons procedure was used to adjust for multiple comparisons; differences between treatments were analyzed using a two-sided Fisher exact test for binomial outcome; treatment differences in DLQI and PSA subscales were analyzed using Wilcoxon rank sum test; for Itching VAS, t-test was used;

Criteria

Inclusion criteria

Age 18 to 75 years; plaque psoriasis for at least 6 months; PASI ≥ 12.0 at screening, at least 10% total body surface area affected, candidate for systemic therapy.

Exclusion criteria

None reported. According to a transcript of a meeting between the FDA and Genentech, patients with psoriasis in flare were excluded.[11]

Permitted co-medications

Emollients, tar and salicylic acid for scalp, low-potency topical glucocorticoids for face, hands, feet, groin, and axillae. All phototherapy and systemic therapy were not allowed.

Results

Patient Characteristics

Characteristic	Placebo (N = 187)	Efalizumab (N = 369)
M/F	71%/29%	68%/32%
Age, mean (range)	45 (20–75)	45 (18–75)
Psoriasis Duration, mean (range)	19 (1–53)	19 (1–62)
Baseline PASI, mean (range)	19 (11–50)	19 (10–59)
Baseline affected BSA, mean (range)	27 (10–90)	28 (10–95)
Previous systemic therapy or phototherapy[†]	139 (74%)	283 (77%)

[†] Genentech reported 59% for placebo and 60% for efalizumab for patients with a history of systemic therapy (excluding phototherapy).[10,11,14]

There were no significant differences among the treatment groups in terms of baseline characteristics.

Patient Disposition

Wks 0–12	PBO	Efalizumab
N (Total = 556)	187	369
Completed treatment	175	345
Discontinued treatment (< 10 doses received)	7	20
Patient's decision	3	7
Adverse events	2	7
Lost to follow-up	5	4
Use of disallowed medication	0	5
Investigator's decision	1	1

Results (cont'd)

Efficacy

Primary efficacy outcome

	Improvement in PASI at week 12	
	≥ 50%	≥75%
Variable	**n / N (%)**	
Placebo	26/187 (14%)	8/187 (4%)
Efalizumab 1mg/kg/wk	216/369 (59%)*	98/369 (27%)*
Treatment difference	—	22.3%
95% CI	—	15.8% to 29.5%

* P < 0.001 vs. placebo

Efalizumab was superior to placebo in terms of PASI-75 (primary end point) and PASI-50 at week 12. The mean PASI improvement at week 12 relative to baseline was 52% on efalizumab and 19% on placebo (p < 0.001).

Secondary efficacy measures

Outcome at week 12	Placebo (N = 187)	Efalizumab (N = 369)
OLS minimal or clear (% of pts)	3%	26%*
PGA excellent or cleared (% of pts)	5%	33%*
DLQI overall score, mean change	14%	47%*
Itching VAS score, mean change	–0.2%	38%*
PSA frequency, mean change	18%	48%*
PSA severity, mean change	17%	47%*

* P < 0.001 vs. placebo

Statistically significant (p < 0.001) improvements in efficacy measures were seen early: at 28 days for DLQI, and at first time point for Itching VAS and PSA frequency and severity.

Safety

Serious adverse events and tolerability

Type of Adverse Event	Placebo (N = 187)	Efalizumab (N = 368)
	n (%)	
Death	0	0
Serious adverse event	1 (1)	9 (2)
Withdrawal adverse event‡	2 (1)	12 (3)

Malignancy was diagnosed in 2 efalizumab-treated patients (1 case each of squamous cell cancer at day 2 and basal cell cancer at day 77); neither case was assessed by investigators as being related to efalizumab.

Statistically significant (p < 0.05) adverse events occurring in at least 5% of all patients

Adverse Event	Placebo (N = 187)	Efalizumab (N = 368)
	n (%)	
Total	133 (71)	296 (80)
Headache	39 (21)	123 (33)
Chills	10 (5)	44 (12)
Myalgia	8 (4)	38 (10)
Pain	9 (5)	37 (10)
Fever	3 (2)	25 (7)
Unintentional injury	19 (10)	17 (5)

The most common adverse events were mild to moderate flu-like symptoms following the first one or two injections.

There was no treatment difference in terms of rate of infections (27% on efalizumab, 23% on placebo). Severe infections occurred in 0.5% of patients in both treatment groups.

No clinically significant laboratory abnormalities were noted. Positive antibodies to efalizumab were detected in 8 patients (2%) on efalizumab and none on placebo. None of these patients experienced serious adverse events or withdrew from treatment.

Conclusions

Efalizumab could provide a viable treatment option for patients with moderate to severe plaque psoriasis.

Critique

Strengths

Good-quality study report (Jadad score, 3); ITT analysis for efficacy; report was critically reviewed in editorial by R. Stern, MD, chairman of the FDA Dermatologic and Ophthalmic Drugs Advisory Committee and member of advisory panel for efalizumab.[16]

Limitations

Randomization method not mentioned; blinding method not detailed; as-treated analysis for safety; duration of therapy (3 months) is inadequate to assess long-term efficacy and safety; study design, size, and duration probably not adequate to detect uncommon but potentially serious adverse events such as malignancies and thrombocytopenia; the study population may not represent a VA population.

Study support and disclosures

First author received research funding from Genentech; second author served as a consultant; four authors employed by Genentech; study sponsored by Genentech; Genentech authors reviewed and edited manuscript.

Citation	**Lebwohl M, Tyring SK, et al. A Novel Targeted T-Cell Modulator, Efalizumab, for Plaque Psoriasis. N Engl J Med 2003;349(21):2004–13.**
Study Goals	To evaluate the efficacy and safety of efalizumab in patients with moderate to severe plaque psoriasis.
Methods	**Study Design** Phase III, multicenter, placebo-controlled, parallel-group, double-blind, randomized trial (study 2059) Three trial phases following 28-day washout of previous antipsoriatic therapy: (1) *First treatment* (weeks 0 through 12)—efalizumab 1 mg/kg/wk, efalizumab 2 mg/kg/wk, vs. placebo (2) *Extended treatment* (weeks 13 through 24)—efalizumab-treated patients were stratified by level of Psoriasis Area and Severity Index (PASI) improvement where patients with PASI ≥ 75 and PASI 50–74 were rerandomized to efalizumab 2 mg/kg/wk, efalizumab 2 mg/kg every other week, or placebo, and patients with PASI < 50 were rerandomized to either efalizumab 4 mg/kg/wk or placebo (3) *Follow-up* (weeks 25 through 36)—treatment was discontinued and patients followed up for 12 wk Randomization used a dynamic approach (urn adaptive biased-coin), balanced within subgroups defined according to baseline PASI (≤ 16 vs. > 16), receipt or nonreceipt of previous systemic treatment for psoriasis, and study site. Blinding was maintained by using two different placebo volumes to match the two doses of efalizumab. Sample size calculated (planned 500: 400 efalizumab, 100 placebo). **Data Analysis** ITT population (all randomized patients) for primary analysis; Hochberg-Bonferroni procedure for multiple comparisons; patients with missing PASI values at week 12 were counted as treatment failures; data for two placebo groups in first treatment phase were combined. Study had > 95% power to detect a difference in the rate of the primary end point at the 0.025 level, assuming a response rate of 25% for efalizumab and 2% for placebo. Primary end point: Proportion of patients who had improvement of at least 75% in the PASI (PASI-75) at week 12 of first treatment phase; comparison of efalizumab with placebo was analyzed by Fisher's exact test Secondary end points: analyzed using two-sample t-tests for continuous variables, Fisher's exact test for dichotomous variables
Criteria	**Inclusion criteria** Age 18 to 70 years; plaque psoriasis that had been clinically stable for at least 3 months and moderate to severe for at least 6 months, PASI of at least 12.0 at screening, plaque psoriasis covering at least 10% of the body-surface area, candidacy for systemic therapy **Exclusion criteria** History of ongoing uncontrolled infection, presence of cancer, history of cancer within the previous 5 years (excluding resolved basal-cell or squamous-cell skin cancers), hepatic or renal dysfunction, white blood cell count less than 4000/mm^3 or greater than 14,000/mm^3, history of severe allergic or anaphylactic reaction to humanized monoclonal antibodies, previous treatment with efalizumab **Withdrawal criteria** Pregnancy, treatment with a live-virus or live-bacteria vaccine, use of systemic or topical therapies for psoriasis (including phototherapy) that were not permitted during study, use of immunosuppressive agents, use of experimental treatments, any medical condition that could jeopardize the patient's safety **Permitted co-medications** Eucerin cream, tar or salicylic acid preparation for psoriasis on the scalp, limited application of low-potency glucocorticoids, oral antipruritic agents

Results

Patient Characteristics (N = 597)

M/F	65%/35%
Age (mean)	46 y
Psoriasis Duration (mean)	19 y
Baseline PASI	20.0
Previous systemic therapy	67%

There were no significant differences among the treatment groups in terms of baseline characteristics.

Patient Disposition

		Efalizumab	
Wks 0–12	**Placebo**	**1 mg/kg/wk**	**2 mg/kg/wk**
N (Total = 597)	122	232	243
Completed phase	111	211	227
Discontinued treatment	11	21	16
Patient's decision	4	8	5
Adverse events	1	7	6
Use of disallowed medication	2	2	3
Lost to follow-up	2	2	2
Investigator's decision	2	2	0

		Efalizumab		
Wks 13–24	**Placebo**	**2 mg/kg/2 wk**	**2 mg/kg/wk**	**4 mg/kg/wk**
N (Total = 434)	145	85	86	118
Completed phase	96	80	78	101
Discontinued treatment	49	5	8	17
Patient's decision	23	3	3	7
Adverse events	18	0	2	8
Use of disallowed medication	5	0	2	1
Lost to follow-up	2	1	0	0
Investigator's decision	1	1	1	1

Efficacy

First-Treatment Phase

	Improvement in PASI at week 12		
	≥ 50%	**≥75%**	**≥ 90%**
Variable	**n / N (%)**		
Placebo	12/122 (16)	6/122 (5)	1/122 (< 1)
Efalizumab 1mg/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)

* P < 0.001 vs. placebo

Efalizumab was superior to placebo in terms of PASI-75 (primary end point) and PASI-50 at week 12.

PASI at week 12 was lower on efalizumab than placebo (9 vs. 17, p < 0.001, post-hoc analysis).

Mean improvement in PASI was 51% for efalizumab 1 mg/kg/wk, 52% for efalizumab 2 mg/kg/wk, and 17% for placebo (p < 0.001 for both comparisons). Treatment differences in terms of improvement in PASI were statistically significant starting at week 4 (p < 0.001 for both comparisons).

Similar responses to that of the overall study population were obtained in subgroups defined by site, sex, age group, baseline PASI, or receipt or nonreceipt of previous systemic therapy.

Extended-Treatment Phase

Efficacy of continued therapy with efalizumab or placebo

	Improvement in PASI at week 24		
	≥ 50%	**≥ 75%**	**≥ 90%**
Variable	**n / N (%)**		
Patients with ≥ 75% improvement at wk 12			
Placebo	16/40 (40)	8/40 (20)	1/40 (2)
Efalizumab 2 mg/kg every other wk	38/49 (95)	31/40 (78)*	13/40 (32)
Efalizumab 2 mg/kg/wk	35/39 (90)	30/39 (77)*	12/39 (31)
Patients with 50%–74% improvement 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)
Patients with < 50% improvement 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)

* P < 0.001 vs. placebo

† P = 0.002 vs. placebo

	‡ P = 0.02 vs. placebo

Results (cont'd)

Efalizumab was superior to placebo in terms of the proportion of patients maintaining an improvement in PASI of 75% or more from week 12 (end of First-Treatment phase) to week 24 (end of Extended-Treatment phase) (77% and 78% vs. 20%; p < 0.001 for both comparisons). Therefore, continued therapy with efalizumab either weekly or every other week was beneficial over stopping active treatment (i.e., starting placebo), and captured an additional 58% (78% – 20%) of PASI-75 responders.

Continued therapy with efalizumab was also superior to placebo in patients with less than 75% improvement in PASI at week 12; however, the rates of capturing additional PASI-75 responders were lower than those seen in the PASI-75 responders at week 12: 25% or 49% among patients who had achieved a partial (50% to 74%) improvement in PASI at week 12, and 11% among patients who had a limited response (50% or less improvement in PASI) in the first 12 weeks.

According to a letter from Genentech Medical Information (November 2003), the proportion of patients with sPGA of minimal or clear at week 12 was 3% on placebo and 19% on efalizumab 1 mg/kg/wk (difference, 16%; 95% CI: 8 to 25; p < 0.001).

In addition, unpublished data presented by the FDA showed that 27 (67%) of 40 patients treated with efalizumab then placebo versus 6 (8%) of 79 patients treated with efalizumab then efalizumab (2 mg/kg weekly or every other week) relapsed.[11,14] Relapse was defined as loss of 50 percent of the improvement achieved during the first 12 weeks of therapy.

Follow-up Phase

At week 36, 12 weeks after discontinuation of treatment, about one third of the patients who had received continuous efalizumab therapy for 24 weeks maintained 50% or more of the improvement that had been achieved during treatment.

The time to relapse among patients who achieved PASI-50 at week 24 was about 84 days. (Relapse was defined as loss of at least 50% of the improvement in the PASI that had been achieved between baseline and week 24.)

Safety

First-Treatment Phase

Serious Adverse Events and Tolerability: No treatment differences

Type of Adverse Event	Placebo (N = 122)	Efalizumab 1 mg/kg/wk (N = 232)	Efalizumab 2 mg/kg/wk (N = 243)	P-value†
	n (%)			
Serious adverse event	1 (1)	4 (2)	7 (3)	0.48
Withdrawal adverse event‡	2 (2)	9 (4)	7 (3)	0.55

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

‡ Adverse event leading to withdrawal from study

Results (cont'd)

Common Adverse Events in First 12 Weeks

Type of Adverse Event	Placebo (N = 122)	Efalizumab 1 mg/kg/wk (N = 232)	Efalizumab 2 mg/kg/wk (N = 243)	P-value[†]
	n (%)			
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 93)	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

Table shows adverse events that occurred in at least 5% of patients in any treatment group and 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 patient were counted once in the overall frequency.

[†] P-values are for the comparisons between the combined efalizumab groups and the placebo group; post hoc, two-sided Fisher's exact tests, without adjustment for multiple comparisons

[‡] Numbers and percentages of patients with at least one adverse event

Acute adverse events were predefined as headache, chills, fever, nausea, and myalgia that occurred within 48 hours of a dose of 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 and subsequent doses, the frequency of acute adverse events was similar between treatment groups.

Extended-Treatment Phase

During the Extended-Treatment phase, compared with the First-Treatment phase:

- acute adverse events were less frequent;
- other adverse events occurred at similar rates;
- withdrawal adverse events were more frequent; and
- infections occurred at similar rates, after adjustment for the season during which treatment was received.

Follow-up Phase

Serious adverse events occurred in 13 patients (3%), including nonfatal infections (5 patients) and psoriasis-related events (3 patients). None of these events led to withdrawal from the study.

Adverse events that occurred in at least 5% of all patients were nonspecific infection (13%), worsening psoriasis (9%), pruritus (6%), and arthritis (5%).

Laboratory Tests

Anti-efalizumab antibodies developed in 5% of patients who were treated with the drug. There were no differences in the safety profile between these patients and those without the antibodies.

Lymphocyte, eosinophil, and total white blood cell counts increased during efalizumab treatment and returned to baseline values after discontinuation of treatment.

Small, transient increases in alkaline phosphatase and serum glutamate pyruvate transaminase concentrations were noted during efalizumab treatment; these were deemed to be not clinically relevant.

Conclusions

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 patients, thus demonstrating the benefit of continued treatment.

(continued)

Critique	**Strengths** Excellent-quality report (Jadad score, 5); ITT analyses **Limitations** Duration of therapy (6 months) may be inadequate to assess long-term efficacy and safety; study design, size, and duration probably not adequate to detect uncommon but potentially serious adverse events such as malignancies and thrombocytopenia; abrupt discontinuation of efalizumab (i.e., continuation with placebo) without instituting other antipsoriatic treatments did not reflect usual clinical practice; response of limited responders (< 50% improvement in PASI after the first 12 weeks of treatment) to continuous treatment with efalizumab at doses other than 4 mg/kg/wk was not assessed and therefore response of limited responders to the recommended 1 mg/kg/wk dose is unclear in this study (but was evaluated in unpublished trials); the study population may not represent a VA population. **Study support and disclosures** The authors reported receiving consulting and lecture fees or grant support from Genentech, Xoma, or other pharmaceutical companies, or had equity ownership or stock options in Genentech, Xoma, or other pharmaceutical companies. Study was supported by Genentech.

Brief Synopsis of Unpublished Phase III Pivotal Extension Trial (Study 2391)

Citation	**Kaiser L. Raptiva (efalizumab) Efficacy [Genentech slide presentation to Food and Drug Administration Dermatologic and Ophthalmic Drugs Advisory Committee, September 9, 2003]. Available at: http://www.fda.gov/ohrms/dockets/ac/03/slides/3983S1_02_D-Genentech-Efficacy_files/frame.htm#slide0002.htm. Accessed 3 December 2003.** **Papadopoulos E. Biologic License Application STN BL 125075/0: Efalizumab for the Treatment of Chronic Plaque Psoriasis [Food and Drug Administration clinical reviewer's slide presentation to Dermatologic and Ophthalmic Drugs Advisory Committee, September 9, 2003]. Available at: http://www.fda.gov/ohrms/dockets/ac/03/slides/3983S1_03_FDA-Efalizumab.ppt. Accessed 10 December 2003.** **BLA-STN 125075/0, Efalizumab (Raptiva). Food and Drug Administration Center for Drug Evaluation and Research, Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (September 9, 2003) [transcript]. Available at: http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3983T1.DOC. Accessed 18 November 2003.**
Study Goals	Not specifically stated in presentations or transcript
Methods	**Study Design** Open-label follow-up to study 2390 **Data Analysis** ITT analysis; evaluation of continued therapy past the initial 12 weeks focused on patients who had received efalizumab in 2390 (N = 369); McNemar's test for PASI-75 and PASI-50 at week 24 versus week 12.
Criteria	**Inclusion criteria** Placebo- and efalizumab-treated patients who completed 2390 were eligible to enroll in 2391 and continue treatment without interruption on efalizumab 1 mg/kg/wk for 12 weeks
Results	**Efficacy** **Efalizumab (N = 369)** **Efficacy Measure** — **Wk 12** — **Wk 24** PASI-75, % of pts — 27% — 44%* PASI-50, % of pts — 59% — 66%* * $p \leq 0.002$, PASI at week 24 vs. week 12 A 24-week course of treatment with efalizumab was significantly better than a 12-week course in terms of the proportion of patients achieving PASI-75 or PASI-50.
Conclusions	Efficacy of efalizumab improves with continued treatment past 12 weeks.
Critique	Patients who entered the extended treatment study tended to be responders only, since nonresponders dropped out of the study.

Acquisition Costs and Cost Analysis

The lowest VA price for a carton of 4 vials (1-month supply) is about $820. The cost for one year of therapy would be $10,654. There is insufficient data to perform a cost analysis.

Data Compilation

NNTs were calculated based on the results of the published (studies 2059 and 2390) and unpublished phase III DB RCTs (from data presented in Table 6 on page 14).

Table 7 Treatment effect of efalizumab: Phase III placebo-controlled DB RCTs

	Published Studies		Unpublished Studies	
	2059	2390	2058	2600
ARR (95% CI)	17% (11 to 24)	22% (16 to 30)	37% (28 to 46)	21% (15 to 27)
NNT (95% CI)	6 (4 to 9)	5 (4 to 6)	3	5

Sources: [9-12,14]
ARR, Absolute Risk Reduction; NNT, Number-needed-to-treat

The NNT range of 3 to 6 means that 3 to 6 additional patients would need to be treated with subcutaneous efalizumab 1 mg/kg weekly rather than placebo for 12 weeks for one additional patient to achieve at least 75% improvement in the PASI.

Conclusions

Efalizumab, an immunosuppressive anti-CD11a monoclonal antibody, is moderately efficacious, relatively safe, and well tolerated as systemic monotherapy in patients with stable moderate to severe plaque psoriasis. Efalizumab should not be considered a disease-remitting agent. As the second biologic agent to be approved for moderate to severe plaque psoriasis, efalizumab offers the potential advantage of self-administered subcutaneous injections, which are more convenient than intramuscular or intravenous injections of alefacept and more available than PUVA and UVB therapies, but less convenient than oral therapies such as methotrexate and cyclosporin. Other potential advantages of efalizumab include lack of lymphopenia and lack of renal, hepatic, or pulmonary toxicity.

The drug appears to be more efficacious as continuous therapy than intermittent therapy and seems to lose efficacy as retreatment for relapsing psoriasis. The loss of efficacy upon retreatment is a unique disadvantage of efalizumab, as this phenomenon is not known to occur with other antipsoriatic treatments. Efalizumab is associated with psoriasis worsening or rebound when treatment is abruptly discontinued without transitioning to alternative therapies. The safety of efalizumab in combination with other therapies and the optimal follow-on therapy after discontinuation of efalizumab are unclear. The long-term risks of thrombocytopenia, malignancies, infections, and autoimmune diseases have not been adequately assessed. The uncertainty of these risks and the lack of data from study patients similar to the veteran population must be weighed against the potential advantages of the drug.

Studies directly comparing efalizumab with other systemic antipsoriatic medications are required to better delineate its place in therapy and relative safety and cost-effectiveness. Further studies are needed to determine the safety and efficacy of efalizumab in other types of psoriasis and as part of combination, rotational, or sequential systemic therapy.

Recommendations

Efalizumab will require specialized review before use and is anticipated to have a low dispensing volume. Alternative systemic immunosuppressive agents for psoriasis (e.g., methotrexate, cyclosporin) are available on the VA National Formulary. Therefore, efalizumab should be nonformulary at both national and VISN levels with criteria for use and restricted to clinicians experienced in the treatment of moderate to severe psoriasis. It should be used as second-line systemic monotherapy in patients with severe plaque psoriasis

who have had an inadequate response, contraindication, intolerance, or hypersensitivity to topical agents, ultraviolet therapy, acitretin, and methotrexate.

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