Biologic Therapies for Psoriasis. A Systematic Review

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ABSTRACT. Alefacept, efalizumab, etanercept, and infliximab are currently approved for the treatment of adults with moderate to severe plaque psoriasis, and phase 3 trials for adalimumab are ongoing. The high level of evidence from large randomized, double-blind, placebo-controlled clinical studies for each of these biologics allows high-grade recommendations and helps define uncertainties, one of which is longterm safety. For tumor necrosis factor-α blocking agents, safety profiles are available from clinical experience in other indications. In general, biologics are safe and effective in the treatment of psoriasis, with potential to address unmet medical needs. Their distinct profiles allow dermatologists to match the biologic agent to individual characteristics of patients who are candidates for systemic therapy or phototherapy. In this evidence-based review of the literature, we assess the effects on psoriasis of induction therapy with 5 biologics and provide preliminary treatment guidelines. (First Release May 15 2006; J Rheumatol 2006;33:1447–51)

Key Indexing Terms:
PSORIASIS ADALIMUMAB ALEFACEPT EFALIZUMAB ETANERCEPT INFLIXIMAB

INTRODUCTION

Although a number of well established therapies are available for psoriasis, unmet clinical needs remain, including longterm safety and practicability. Biologics, defined as molecular species generated in cell-based systems, have the potential to meet these needs[1]. Major trials evaluating biologics in psoriasis have focused on moderate to severe plaque-type psoriasis, which is present in 80% of adult patients[2] and is characterized by thickened, well demarked, red plaques, covered with silvery-white scales, which are often itchy, causing discomfort and distress. Psoriasis can reduce patients' overall health and well-being to a degree comparable to other major clinical diseases such as cancer or arthritis[3].

The pathogenesis of psoriasis has been reviewed elsewhere[2]. In summary, psoriasis is currently regarded as an immune-mediated inflammatory disease. Antigen-presenting dendritic cells of the epidermis transport yet unknown antigens to regional lymph nodes and present them to naive T cells. These respond by activation, proliferation, and maturation into effector T cells, which patrol the body and leave circulation at the site of antigen contact. Subsequently, these cells migrate toward the epidermis and upon reactivation, release effector molecules, namely proinflammatory cytokines such as tumor necrosis factor-α (TNF-α).

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Outcome Measures

Measures currently used to document therapeutic efficacy include determination of the affected body surface area (BSA), Psoriasis Area and Severity Index (PASI), and the Dermatology Life Quality Index[4]. In the absence of a precise definition, moderate to severe psoriasis is considered to be characterized by scores > 10 in any of these instruments[5]. Treatment success is defined by reduction of the respective scores. Typically, the percentage of patients achieving at least a 75% reduction in the PASI (PASI75) is considered a good clinical response.

Search Strategy

This search was focused on induction therapy for plaque-type psoriasis. A systematic search of Medline was started in June 2004 and updated in November 2005. The evidence referenced here was graded as described by Kavanaugh and Ritchlin[6].

RESULTS

Adalimumab. Adalimumab is a recombinant, fully human IgG1 monoclonal antibody specific for human TNF-α that binds and neutralizes TNF-α. Adalimumab is approved by the US Food and Drug Administration (FDA) for use in psoriatic arthritis (PsA).

Published data are limited to the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT)[7], in which 69/151 patients with psoriasis affecting BSA ≥ 3 received adalimumab (level 1B, grade A). Data from a phase 2 trial involving 148 patients with psoriasis have been published as part of reviews[8].

Patients in the ADEPT received subcutaneous (SC) injections of 40 mg adalimumab every other week; whereas patients in the psoriasis trial received either a loading dose of 80 mg followed by 40 mg every other week, or weekly injec-

tions of 80 mg for 2 weeks and 40 mg thereafter. In the ADEPT, 59% of adalimumab-treated patients achieved a PASI75 after 24 weeks. In the psoriasis study, 53% of patients receiving the 80 mg loading dose followed by 40 mg every other week achieved a PASI75 at Week 12, compared with 80% of patients receiving 80 mg weekly for 2 weeks followed by 40 mg weekly.

Adalimumab was generally well tolerated, with similar rates of adverse events in treatment and placebo groups. The primary side effect was pain at the injection site. Other common adverse events included upper respiratory infections, headache, and nausea.

Additional longterm safety information is available from several trials in rheumatoid arthritis (RA)[9,10], where overall rates of adverse events were similar between adalimumab and placebo groups. Because 13 cases of tuberculosis have been reported, screening for latent tuberculosis is recommended. The standard incidence ratio for lymphoma was significantly different from the general population; however, patients with RA clearly have an increased risk of lymphoma. Recently, the FDA reviewed lymphoma cases in association with anti-TNF therapies, and observed no obvious increase in the incidence of lymphoma in RA patients treated with these agents, but recommended continued monitoring.

Alefacept. Alefacept is a dimeric fusion protein consisting of the extracellular CD-2 binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the constant portion of a human IgG1 antibody. By blocking LFA-3/CD-2 interaction, alefacept inhibits T cell activation and proliferation and induces apoptosis of memory T cells. Alefacept is approved by the FDA for treatment of psoriasis, but is not currently approved by the European Agency for the Evaluation of Medicinal Products (EMEA).

Publications of 3 studies on a total of 1288 patients fulfilled the search criteria (level 1B, grade A)[11-13]. In 2 studies of 782 patients, alefacept was administered intravenously (IV) weekly for 12 weeks, either over one treatment course at doses of 0.025, 0.075, or 0.15 mg/kg body weight, or over 2 treatment courses at a fixed dose of 7.5 mg/kg[14,15]. A third study analyzed intramuscular (IM) application of 10 and 15 mg weekly over 12 weeks in 507 patients[13].

Efficacy of alefacept was dose-dependent and relatively low and slow, but PASI75 was reached by up to 33% of patients at some point (about 20% PASI75 at Week 12). Clinical improvement continued after the initial 12-week treatment course, reached a maximum at Week 14, and improved slightly during a second treatment course, resulting in a prolonged phase of improved skin symptoms in patients with PASI75 after the initial course[11-13].

Alefacept was generally well tolerated. Adverse events were comparatively rare and mild (including headache, infection, and accidental injuries), with similar rates in the treatment and placebo groups. Dropout rates reached 15%, but usually were not due to adverse effects. Because reduction in CD4+ T cell counts was occasionally observed, monitoring of CD4+ cells is required, and treatment should be discontinued if the CD4+ T cell count drops below 250/μl.

Efalizumab. Efalizumab is a humanized monoclonal antibody targeting the CD11a component of leukocyte function-associated antigen-1, preventing its binding to intercellular adhesion molecules. Blocking this interaction results in interference with T cell activation and reactivation, inhibition of leukocyte extravasation, and adherence to keratinocytes in lesional psoriatic epidermis. Efalizumab is approved by the FDA and EMEA for treatment of psoriasis (see Discussion).

Five studies from a total of 2352 patients were evaluated (level 1B, grade A)[14-18]. Additionally, data from an open-label trial for maintenance therapy (15 months) were considered[19].

Optimal efficacy with efalizumab was seen with weekly SC doses of 1 mg/kg (PASI75 in 22%–39% of patients within 12 weeks)[14-17]. Similar efficacy was observed in "high-need" patients, where at least one systemic therapy had failed or was contraindicated. Patients achieving less than PASI50 after 12 weeks did not benefit significantly from continued therapy, whereas about one-third of patients with an outcome between PASI50 and PASI75 reached at least a PASI75 response after 12 more weeks of treatment[15,16]. Continuation of therapy resulted in additional clinical improvement.

Efalizumab was generally well tolerated, with similar rates and types of adverse events in the active and placebo groups. Injection site reactions were the most frequently seen adverse event, presenting mainly as flu-like symptoms after the first and second injections, and could be controlled by decreasing the dose or with nonsteroidal antiphlogistics. Termination of therapy was observed to cause rebound in some 15% of patients with low initial responses, but occurred less frequently (about 1%) in patients with a good clinical response and could be prevented by adding other therapies[20]. Leukocytosis was observed frequently, but stayed within physiologic limits and resolved after termination of treatment. Thrombocytopenia was observed occasionally, as were single cases of hemolytic anemia; thus, monitoring should include platelet counts. Dropout rates were about 10%, but usually were not due to adverse effects. The risk for adverse events did not increase throughout a 15-month observation period[19].

Etanercept. Etanercept is a fusion protein consisting of the extracellular ligand-binding portions of 2 human TNF receptors and the Fc portion of a human IgG1 antibody, which together exhibit higher affinity to TNF-α than the naturally occurring monomeric TNF receptors. TNF-α bound to etanercept is functionally inactive, and its proinflammatory effects are blocked. Etanercept is approved by the FDA and EMEA for treatment of psoriasis (see Discussion).

Publications of 4 studies on a total of 1007 patients were analyzed (level 1B, grade A). Two studies were conducted in patients with moderate to severe plaque-type psoriasis[21,22]. Two other studies were performed in patients with PsA, where 166/265 had > 3% BSA affected[23,24]. In all studies, etanercept

was administered SC over 12 or 24 weeks at 1 × 25 mg, 2 × 25 mg, or 2 × 50 mg per week.

In psoriasis studies, etanercept efficacy was dose-dependent, with a PASI75 response observed in 34% of patients in the 2 × 25 mg weekly group, and in 50% of patients in the 2 × 50 mg group at Week 12. An additional 12 weeks of treatment improved the efficacy (PASI75 up to 59%) at the 2 × 50 mg dose, which is the recommended regimen according to expert consensus[8]. Treatment beyond 24 weeks results in further improvement of efficacy (data on file at Wyeth). The European label, however, requires etanercept to be discontinued after 24 weeks. Tachyphylaxis is absent in retreatment.

Studies in PsA patients showed lower efficacies. Differences in PASI75 between studies in psoriasis (seemingly higher efficacy) and PsA (seemingly lower efficacy) may be explained by a systematic bias of the PASI in milder forms of psoriasis resulting in underestimation of improvement; the mean PASI was lower in PsA trials compared with psoriasis trials. Additionally, because many patients with PsA were allowed to continue methotrexate treatment, their skin symptoms may be biased toward not responding to methotrexate and therefore more recalcitrant.

Etanercept was generally well tolerated, with comparable rates and types of adverse events (mainly flu-like symptoms) in the active and placebo groups. Additionally, etanercept frequently caused mild injection site reactions. Infections, mainly of the upper respiratory tract, bronchitis, or skin infections, also occurred. Dropout rates in the studies were approximately 10%, but were not due to adverse effects.

Longterm safety data are available from patients treated for other indications, particularly RA. A slight increase in tuberculosis has been observed in these patients. Given the higher prevalence of tuberculosis in Europe compared to the US, a German S1 guideline advises physicians to exclude tuberculosis testing in patients when etanercept is considered for psoriasis treatment. A study of 1960 patients with RA treated with etanercept for 5 years showed similar rates of infections requiring hospitalization or IV antibiotics, compared with patients not receiving etanercept[25]. No increased incidence of malignancies was observed in several studies in RA or psoriasis (Wyeth product information).

Infliximab. Infliximab is a chimeric monoclonal antibody directed against TNF-α, comprising the murine TNF-binding portion and human IgG1, which binds and neutralizes both soluble as well as receptor-bound TNF-α. Moreover, infliximab mediates lysis of TNF-producing cells. Infliximab is approved by the FDA and EMEA for treatment of psoriasis (see Discussion).

Publications of 3 studies of a total of 315 patients with moderate to severe plaque-type psoriasis were analyzed (level 1B, grade A)[26,28]. Infliximab was administered IV at a dose of 3, 5, or 10 mg/kg body weight at Weeks 0, 2, and 6. Additionally, 2 large phase 3 trials in PsA[29,30] evaluated the PASI in 122/304 patients with significant skin involvement. Finally, a trial of 378 patients in maintenance therapy was recently published[31].

Infliximab efficacy in psoriasis studies was high and rapid, with a PASI75 response at Week 10 in about 70% of patients treated with the 3 mg/kg dose and up to 88% with the 5 mg/kg dose. Of note, about 50% of patients experienced a PASI90 response at Week 10. Significant improvement was seen as early as the second infusion. Efficacy did not increase with the higher 10 mg/kg dose. As with etanercept trials, the efficacy of infliximab on psoriasis in the 2 PsA trials (IMPACT 1 and 2) was lower.

Infliximab was generally well tolerated, with upper respiratory infections the most frequent adverse event. Other frequent events were acute infusion reactions, which were usually mild, with shivering, headache, flush, nausea, or dyspnea, and were managed by slowing or interrupting the infusion rate. Since anaphylactoid reactions may occur, close patient monitoring is advised. Rarely, delayed infusion reactions were reported, causing serum sickness 3–12 days after infusion. Rare cases of severe liver toxicity or even lethal liver failure have been observed, occurring within 2 weeks to one year after treatment initiation. Thus, infliximab therapy should be stopped upon jaundice or significant elevation of liver enzymes. Dropout rates were about 10%; reasons could not be identified from published data.

Longterm safety data are available from infliximab treatment in other indications. Important adverse events comprise infections, including opportunistic infections and tuberculosis; tuberculin skin testing is therefore a prerequisite for initiation of therapy. Other rare adverse events include demyelinating diseases, worsening of cardiac insufficiency, leukopenia, thrombopenia, pancytopenia, and reversible lupus-like syndrome.

DISCUSSION AND CONCLUSIONS

Four biologics are currently approved for the treatment of plaque-type psoriasis. Per FDA approval, efalizumab, etanercept, and alefacept are indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. Per EMEA approval, efalizumab, etanercept, and infliximab are indicated if patients fail to respond to, or have a contraindication to, or are intolerant of other systemic therapy. Whereas European authorities consider biologics to be second- or last-line therapeutics in this indication, expert consensus agrees with FDA labeling.

Although head-to-head comparative studies among biologics are lacking, the trials referenced here highlight their distinct profiles (see Table 1). Per guidelines recently published by the British Association of Dermatology[32], the choice of biologic therapy should include the following criteria:

- Efalizumab is favorable in patients with high risk of latent tuberculosis or evidence of demyelinating disease

Table 1. Biologic treatments for psoriasis.

Study	Agent	Study Type	No. of Patients	Dosing	Results	Comments
Patel[8]	Adalimumab	RDBPC	148	Loading dose of 80 mg SC followed by 40 mg every other week vs 2 doses of 80 mg SC followed by 40 mg every week	PASI75 after 12 weeks: 53% vs 80%	Publication refers to abstract publications
Mease[7]	Adalimumab	RDBPC	69	40 mg SC every other week	PASI75 after 12 weeks: 59%	ADEPT (PsA/Ps): 69/151 patients were evaluated by PASI
Ellis[11]	Alefacept	RDBPC	229	0.025 vs 0.075 vs 0.150 mg/kg weekly IV for 12 weeks	PASI75 after 14 weeks: 21% vs 33% vs 31%	
Krueger[12]	Alefacept	RDBPC	553	7.5 mg weekly IV for 12 weeks	PASI75 after 14 weeks: 14%	Trial designed to evaluate multiple courses of treatment
Lebwohl[13]	Alefacept	RDBPC	507	10 mg vs 15 mg weekly IM for 12 weeks	PASI75 at any point throughout treatment: 28% vs 33%	Data on file suggest approx. 20% of patients achieve PASI75 after 12 weeks
Gordon[14]	Efalizumab	RDBPC	556	1 mg/kg weekly SC	PASI75 after 12 weeks: 27%	
Gottlieb[19]	Efalizumab	Open-label	339	2 mg/kg weekly SC with/without topical steroid	PASI75 after 9–12 weeks: ~40%	Maintenance study
Lebwohl[15]	Efalizumab	RDBPC	597	1 vs 2 mg/kg weekly SC	PASI75 after 12 weeks: 22% vs 28%	
Leonardi[16]	Efalizumab	RDBPC	498	1 vs 2 mg/kg weekly SC	PASI75 after 12 weeks: 39% vs 27%	
Menter[17]	Efalizumab	RDBPC	556	1 mg/kg weekly SC	PASI75 after 12 weeks: 27%	
Papp[18]	Efalizumab	RDBPC	145	0.1 vs 0.3 mg/kg weekly IV	PASI after 56 days: 5% vs 25%	Dose-finding study
Gottlieb[21]	Etanercept	RDBPC	112	2 × 25 mg weekly SC	PASI after 12 weeks: 30%	
Leonardi[22]	Etanercept	RDBPC	672	1 × 25 mg vs 2 × 25 mg vs 2 × 50 mg weekly SC	PASI after 12 weeks: 14% vs 34% vs 49%	Dose-finding study
Mease[23]	Etanercept	RDBPC	38	2 × 25 mg weekly SC	PASI after 12 weeks: 26%	PsA/Ps study: 38/60 patients evaluated by PASI
Mease[24]	Etanercept	RDBPC	128	2 × 25 mg weekly SC	PASI after 24 weeks: 23%	PsA/Ps study: 128 patients evaluated by PASI
Antoni[29]	Infliximab	RDBPC	39	5 mg/kg IV at Weeks 0, 2, 6, and 14	PASI75 after 16 weeks: 68%	IMPACT 1 (PsA/Ps): 39/104 patients evaluated by PASI
Antoni[30]	Infliximab	RDBPC	83	5 mg/kg IV at Weeks 0, 2, and 6	PASI75 after 14 weeks: 64%	IMPACT 2 (PsA/Ps): 83/200 patients evaluated by PASI
Gottlieb[28]	Infliximab	RDBPC	249	3 vs 5 mg/kg IV at Weeks 0, 2, and 6	PASI75 after 10 weeks: 72% vs 88%	PASI90 achieved by around 50%
Chaudhari[26]	Infliximab	RDBPC	33	5 vs 10 mg/kg IV at Weeks 0, 2, and 6	PASI75 after 10 weeks: 82% vs 73%	

IV: intravenous; IM: intramuscular; PsA: psoriatic arthritis; Ps: psoriasis; RDBPC: randomized, double-blind, placebo-controlled; SC: subcutaneous.

- Infliximab is advantageous where rapid disease control is required (e.g., unstable erythroderma)
- Etanercept is the biologic of choice in stable psoriasis where a TNF-α-blocking strategy is appropriate.

All biologics approved to date for the treatment of psoriasis are recommended for patients who are candidates for systemic or phototherapy; therefore, the decision to use biologics must be made by a dermatologist with careful regard to the treatment options applicable to each individual patient. Some biologics are also approved for treatment of PsA; thus, patients with PsA may benefit from a biologic for both the articular and dermatologic manifestations of their disease, even if their psoriasis is mild. Additional therapy with topical antipsoriatics is encouraged.

Most trials with biologics in psoriasis focused on induction therapy. The chronic-recurrent course of the disease, however, may be more appropriately managed with a longterm maintenance regimen. The safety of longterm treatment with biologics has yet to be reported in patients with psoriasis, and where additional data are available from other indications, the conclusions must be interpreted carefully. Further research is needed to evaluate the safety, efficacy, and pharmacoeconomic aspects of longterm management of psoriasis with biologics.

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