Biologic agents in psoriasis

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SUMMARY

This paper reviews the new biologic agents that selectively block the immunologic steps implicated in the pathogenesis of psoriasis. Four strategies have been targeted: reduction of the number of pathogenic T cells; inhibition of T-cell activation and migration; modulation of the immune system; and blockage of the activity of inflammatory cytokines. There are three classes: monoclonal antibodies, fusion proteins and recombinant cytokines or growth factors. The actions, efficacy and side-effect profile of the biologic agents, alefacept, efalizumab, etanercept and infliximab, are reviewed.

Key words: alefacept, efalizumab, etanercept, fusion protein, infliximab, monoclonal antibody, psoriasis area and severity index, recombinant cytokine.

INTRODUCTION

There is currently an unmet need for a treatment for psoriasis that is readily available, safe, efficacious, and provides long-term remission. Advances in molecular biotechnology have resulted in the emergence of new targeted biologic therapies in dermatology, in parallel with other areas in medicine. These new biologic agents have yielded tangible results that meet some of the criteria of the ideal therapy. They offer the hope for safe, long-term control of psoriasis because, to date, biologics have no known nephrotoxicity or hepatotoxicity. It is desirable for drugs to have the least global immunosuppression in treating psoriasis and biologics selectively block immune pathways implicated in the pathogenesis. This paper reviews the new biologic agents in the context of these cellular and molecular immune pathways.

IMMUNOMODULATION BY BIOLOGIC THERAPY

The US Department of Health and Human Services defines ‘biologic response modifiers’ as a generic term for hormones, neuroactive compounds and immunoreactive compounds that act at the cellular level. The FDA Centre for Biologics Evaluation and Research defines biologics as those agents derived from living material: human, plant, animal or microorganism. There are three distinct classes of biologic agents: monoclonal antibodies, fusion proteins and recombinant cytokines or growth factors. Antibodies can be classified as chimeric where the antibody is composed of human and murine sequences, humanized where individual amino acids in a human backbone are replaced with specific murine sequences, or human sequence. Fusion proteins consist of a human receptor domain, so it has capacity to bind to its ligand, which is fused to the constant portion of IgG thus allowing solubility in plasma. A strict nomenclature for the generic names of the biologics has been developed. Generic names of chimeric monoclonal antibodies have the suffix -ximab, humanized monoclonal antibodies have the suffix -zumab and human monoclonal antibodies have the suffix -umab. Receptor–antibody fusion proteins have the suffix -cept. The strategies for immunomodulation in psoriasis are outlined in

Abbreviations:

CD cluster of differentiation
DLQI dermatology life questionnaire index
FDA Food and Drug Administration
IFN interferon
Ig immunoglobulin
IL interleukin
iNOS inducible nitric oxide synthase
LFA lymphocyte function associated antigen
PASI psoriasis area and severity index
PGA physician’s global assessment
PSA Psoriasis Symptom Assessment
TGA Therapeutic Goods Administration
Th T-helper
TNF tumour necrosis factor

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Table 1. Evidence is lacking for the use of biologics in pregnancy and lactating mothers. Therefore, these agents should not be used in pregnant or lactating mothers. It is advised that women of child-bearing potential should use contraception during treatment.

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Figure 1 Actions of alefacept: (1) The LFA-3 portion binds to CD2 on the surface of T cells and blocks the interaction of CD2 with natural LFA-3. (2) The IgG1 portion binds to the FcγRI and FcγRIII receptors of NK cells or monocytes, inducing granzyme-mediated apoptosis of memory effector T cells. This illustration has been provided by Biogen Idec. APC, antigen presenting cell; CD, cluster of differentiation; IgG1, immunoglobulin G1; LFA, lymphocyte function associated antigen; MHC, major histocompatibility complex; NK, natural killer; TCR, T-cell receptor.

Table 1. Evidence is lacking for the use of biologics in pregnancy and lactating mothers. Therefore, these agents should not be used in pregnant or lactating mothers. It is advised that women of child-bearing potential should use contraception during treatment.

Strategy 1: Reduction of the number of pathogenic T cells

Alefacept, LFA-3TIP (Amevive; Biogen Idec, Cambridge, MA, USA) is a fusion protein combining two binding sites of LFA-3 with the hinge, CH2 and CH3 sequences of IgG1. The LFA-3 segment binds to CD2 on memory T cells (Fig. 1), thereby inhibiting the activation and proliferation of T cells. CD2 is constitutively expressed on all T-lymphocytes; however, it is up-regulated on the surface of memory T cells. The constant portion of IgG1 additionally binds to FcγRII/CD16 on natural killer cells and monocytes which triggers granzyme-mediated apoptosis of those T cells expressing high levels of CD2 (Fig. 1). Since CD45RO+ memory effector T cells express more CD2 than do CD45RA+ naïve T cells, alefacept binds preferentially to memory effector T cells. Alefacept is currently approved by the TGA in Australia for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic agents or phototherapy.

Alefacept is administered intramuscularly. The recommended regimen is a 12-week course of weekly injections (15 mg). This is then followed by a 12-week rest period and a subsequent second course comprising weekly injections (15 mg) for a further 12 weeks may be considered. The results of a phase IV multicentre study in five sites within Australia to determine whether patients with chronic plaque psoriasis are able to go beyond the second 12-week rest period before requiring alefacept or an alternative therapy in patients are eagerly anticipated. It is recommended that a baseline CD4+ T-lymphocyte count be performed and fortnightly thereafter. Should the CD4+ counts fall below 250 cells/mL, then dosing should be withheld until CD4+ counts recover. If the CD4+ counts continuously remain below 250 cells/mL for four consecutive weeks, then the drug should be ceased.

In a randomized, double-blind, placebo-controlled phase III study, the clinical efficacy of alefacept given intramuscularly was demonstrated. A total of 507 patients were randomized to receive i.m. placebo (n = 168), 10 mg of alefacept (n = 175) or 15 mg of alefacept (n = 166) weekly for 12 weeks followed by 12 weeks of observation. Throughout
the study, a significantly \( P < 0.001 \) higher percentage of patients in the 15 mg group (33%) or 10 mg group (28%) than in the placebo group (13%) achieved at least 75% PASI reduction from baseline. The percentage of patients achieving at least 50% reduction in PASI throughout the study period was 57% in the 15 mg alefacept group compared with 55% in the placebo group \( (P < 0.001) \). The same endpoint was achieved by 55% of patients in the 10 mg alefacept group \( (P = 0.002 \text{ vs placebo}) \).

The results of the clinical trials have shown that alefacept significantly improves the symptoms of psoriasis. In the phase III trials, the DLQI was compared to the PGA status and PASI scores.\(^8\) Those who achieved a PGA status of ‘clear or almost clear’ and at least a 75% reduction in the PASI score from baseline achieved a >70% improvement in DLQI scores. Those with at least a 50% reduction in the PASI score from baseline also demonstrated a marked improvement (60%) in their DLQI score.

While the onset of action is slow, a major benefit of alefacept is that it has the potential for long-term remission. The clinical response to alefacept has shown to be durable during follow up. It has been demonstrated that of those who receive 12 weeks of 15 mg intramuscular alefacept, 74% are able to maintain at least a 50% reduction in PASI during the 12-week follow-up period. Of those who receive 15 mg intramuscular alefacept and achieve a 50–75% PASI reduction from baseline 2 weeks after the last dose, 79% maintain at least a 25% reduction in PASI during the 12-week follow-up period.\(^7\)

Adverse events reported from clinical trials include headache, pruritus, infection, rhinitis, injection site pain and injection site inflammation.\(^7,9,10\) The trials have shown that alefacept does cause transient decreases in CD45RO+ memory T cells.\(^7,9,10\) Alefacept does not interfere with the primary and secondary responses to a newly encountered antigen and the acquired immune response to a recall antigen.\(^11\)

Whether problems occur with continuous courses longer than 12 weeks remains to be seen. These results are encouraging because one of the concerns of other immunosuppressive therapies is that they are non-specific in terms of targeting particular T-cell subsets. Biogen Idec has reported that two of the 1557 patients treated with alefacept developed lymphoma (Hodgkin and folliculo-centric lymphoma) while on or after ceasing alefacept.\(^8\) These patients had been treated with various systemic agents before starting alefacept. The clinical data demonstrate that alefacept exhibits a low potential for immunogenecity and there were no reports of hypersensitivity in those few patients that did develop antialefacept antibodies.\(^7,9\)

**Strategy 2: Inhibition of T-cell activation and migration**

**Efalizumab** (Baptiva; Genentech and XOMA, South San Francisco, CA, USA) is a humanized form of a murine antibody targeted against CD11a, a subunit of LFA-1. Lymphocyte function associated antigen-1, composed of the subunits CD11a and CD18, is responsible for T-cell activation, cytotoxic T-cell function, and T-cell adhesion to keratinocytes and vascular endothelium.\(^12,13\) Efalizumab can therefore interfere with development of psoriatic plaques by blocking T-cell migration into the skin and by inhibiting T-cell activation (Fig. 2).

Efalizumab is currently approved by the TGA in Australia for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic agents or phototherapy. Efalizumab is administered subcutaneously. The recommended dose is 0.7 mg/kg for the ini-

![Figure 2](https://example.com/efalizumab-diagram.png)

**Figure 2** Efalizumab inhibits T-cell activation, cytotoxic T-cell function, and T-cell adhesion to keratinocytes and vascular endothelium by targeting against CD11a, the subunit of lymphocyte function associated antigen-1. This illustration has been provided by Serono. CD, cluster of differentiation; ICAM, intercellular adhesion molecule; LFA, lymphocyte function associated antigen.
tial dose followed by 1 mg/kg weekly thereafter. Treatment is of a continuous nature.

In a phase III, randomized, double-blind, parallel group, placebo-controlled, multicentre, 12-week study, \(^{16}\) weekly subcutaneous efalizumab (1 mg/kg) improved psoriasis. Efalizumab therapy resulted in significant improvements in PASI scores, PGA, overall DLQI, Itching Visual Analog Scale (ranges from 0 [no impairment] to 10 [severe itching]) and PSA score. By week 12, 27\% of efalizumab-treated patients achieved a PASI-75 response compared with 4\% of placebo-treated patients \((P < 0.001)\). Patients in the efalizumab group showed improvement in the mean DLQI scores by the second week compared with the placebo group \((P < 0.001)\). Efalizumab-treated patients reported greater improvements in their attitudes about their disease, their ability to participate in daily activities (including leisure and work) and their personal relationships. There was a trend towards improvement across all symptoms in both frequency and severity in the efalizumab group as shown by mean improvements in the PSA score. With respect to severity, or how bothersome the symptoms were, the largest absolute improvements occurred in both the itching (mean improvement of 1.1 for efalizumab vs 0.3 for placebo \([P < 0.001]\)) and scaling (1.2 for efalizumab vs 0.4 for placebo \([P < 0.001]\)) components.

In a phase III, multicentre, randomized, placebo-controlled, double-blind study, extending efalizumab treatment from 12 to 24 weeks demonstrated ongoing benefit. \(^{13}\) The study involved three consecutive phases: the first treatment phase (weeks 0–12), the extended treatment phase (weeks 13–24) and the follow-up phase (weeks 25–36). In the first phase, patients were randomized to 1 mg/kg subcutaneous efalizumab per week, 2 mg/kg subcutaneous efalizumab per week, or placebo. In the second phase, subjects who had received efalizumab were stratified into three subgroups based on their week 12 PASI score improvement from baseline (≥75%, 50–74%, or <50%). Subjects in the first two strata were randomized to 2 mg/kg of efalizumab either weekly or every other week or to placebo. Subjects in the third stratum (<50% improvement) were randomized to either an increased dose of efalizumab 4 mg/kg per week or placebo. Those randomized to placebo in the first phase were discontinued after week 12. At week 12, there was at least a 75% improvement in the PASI score from baseline of 22\% in those who had received 1 mg/kg of efalizumab per week, 28\% in those who had received 2 mg/kg of efalizumab per week as compared with 5\% of those who received placebo \((P < 0.001)\) for both comparisons. Efalizumab-treated patients had greater improvement than those receiving placebo as early as week 4 \((P < 0.001)\). Continued efalizumab therapy provided continued benefit. Among the efalizumab group who had an improvement of at least 75\% in their PASI scores from baseline at week 12, improvement was maintained through week 24. At week 56, 12 weeks after the discontinuation of efalizumab, at least 50\% improvement in the PASI scores from baseline achieved during treatment was maintained in 50\% of the subjects who had received continuous efalizumab for 24 weeks. The time to relapse (loss of at least 50\% of the improvement in PASI score that had been achieved between baseline and week 24) among subjects who had an improvement of at least 50\% at week 24 was approximately 84 days.

Long-term administration of efalizumab is currently being evaluated in an ongoing open-label, phase III study. \(^{16}\) In the initial 12-week treatment period, patients received weekly subcutaneous efalizumab 2 mg/kg. Patients who achieved at least a 50\% improvement in their PASI score from baseline or an overall PGA grading of mild, minimal or clear were eligible to enter the open-label maintenance period, comprising an additional 33 months of treatment. During maintenance treatment, the subjects received weekly doses of subcutaneous efalizumab 1 mg/kg and in the event of relapse (loss of at least 50\% improvement in their PASI score from baseline at month 5), the dose was increased to 2, 3 or 4 mg/kg weekly. At 12 weeks, 41\% and 82\% of patients achieved at least a 75\% or 50\% improvement in their PASI score from baseline, respectively. At 15 months, 50\% and 65\% of patients achieved at least a 75\% or 50\% improvement in their PASI score from baseline, respectively.

The most frequent adverse events reported in the clinical trials were fever, nausea, vomiting, headaches, chills, asthenia, myalgia and pharyngitis. \(^{14–19}\) These occurred on the day or within 2 days after the administration of the drug and were most frequent after the first dose and decreased in frequency over time and by the third dose, the percentage of these adverse events were similar to placebo. Transient increases in circulating T-lymphocytes were noted in the efalizumab-treated group during studies and returned to reference range upon completion of treatment. \(^{15,16,18,19}\) Treatment with efalizumab has been associated with thrombocytopenia. Therefore, platelet counts are recommended every month for the first 5 months and every 5 months thereafter. One major concern with the use of efalizumab is the rebound of psoriasis. Formulating a plan of transition to address the issue of rebound before discontinuing efalizumab is necessary. A post-hoc analysis of the effectiveness of treatments in preventing rebound during the observation period from 1014 participants in the phase II and III trials showed that cyclosporin was completely successful in preventing rebound. High-potency topical corticosteroids were shown to be successful with only 7\% (8/111) of patients achieving rebound status. The least helpful strategies included psoralen and UVA and systemic retinoids with rebound rates of 25\% (2/8) and 21\% (5/24), respectively. \(^{20}\)

**Strategy 5: Modulation of the immune system**

Two distinct lines of T-cell differentiation are possible. Under the influence of IL-12 and IFN-γ, CD4 T cells differentiate into a Th1 phenotype and CD8 T cells differentiate into a Th1 phenotype. Both of these phenotypes produce type-1 cytokines which include IL-1α, IL-1β, IL-2, IL-6, IL-8, IFN-γ, TNF-α and TNF-β, TGF-α and TGF-β, and granulocyte colony stimulating factor. \(^{21–25}\) Psoriasis is characterized by an over-expression of the pro-inflammatory type-1
cytokines. Alternatively, under the influence of IL-4, IL-6 and IL-10, CD4 T cells differentiate into a Th2 phenotype and CD8 T cells differentiate into a Te2 phenotype. Both of these phenotypes produce type-2 cytokines which include IL-4, IL-6, IL-10 and IL-11.\textsuperscript{26,27} An alternative strategy to blocking the immunological process is to deviate the immune response to a type-2 cytokine pattern.

**Ilodecakin** (Tenovil, Schering-Plough, Berlin, Germany), a human recombinant IL-10, is an important Th2-cytokine that is responsible for the down-regulation of the Th1-cytokine response (IL-2, IL-12, TNF and IFN-\(\gamma\); Fig. 5).\textsuperscript{21–23} There is a relative deficiency of IL-10 in psoriasis.\textsuperscript{27} In a double-blind, placebo-controlled study,\textsuperscript{28} seven patients received human recombinant IL-10 subcutaneously (10 \(\mu\)g/kg) three times per week until relapse or study termination after 4 months. Remission (defined as PASI < 5) was achieved by UV light (type not specified) in combination with topical calipotriol and/or topical dithranol before entry into the study. Nine of 10 in the placebo group and only two of seven in the human recombinant IL-10-treated group showed a relapse during the observation period (\(P < 0.05\)). Moreover, the mean duration of remission in the human recombinant IL-10 group was higher than in the placebo group (101 days vs 66.4 days). Several other studies report improvements in skin lesions.\textsuperscript{27,28,31} However, in a randomized, double-blind, placebo-controlled trial\textsuperscript{32} involving 28 patients, 18 patients treated with subcutaneous human recombinant IL-10 (20 \(\mu\)g/kg) three times weekly for 12 weeks resulted in only temporary clinical improvement. The mean percentage improvement in PASI scores from baseline at week 8 for the human recombinant IL-10-treated group was significantly higher than that for the placebo group (36% vs 15.3%, \(P = 0.05\)). However, most patients receiving human recombinant IL-10 experienced a rebound following week 8 as reflected in the mean percentage improvement in PASI scores from baseline at week 12 despite sustained decreases in pro-inflammatory type-1 cytokine production (17% for the human recombinant IL-10 treated group vs 12.9% for the placebo group, \(P = 0.69\)). Treatment with human recombinant IL-10 has been shown to lead to anaemia, thrombocytopenia and a reduction in serum cholesterol. Studies for ilodecakin are ongoing.

**Oprelvekin** (Neumega; Genetics Institute, Cambridge, MA, USA) is a human recombinant IL-11 and has demonstrated improvement in psoriasis in seven of 12 patients when administered daily subcutaneous injections for 8 weeks in an open-label, phase I dose escalation study.\textsuperscript{33} Intraepidermal T cells and total lesional T cells are reduced and synthesis of intercellular adhesion molecule-1 by epidermal keratinocytes is eliminated by human recombinant IL-11. In addition, IL-11 decreases the expression of the products of disease-related genes, including keratin 16, inducible nitric oxide synthase, IFN-\(\gamma\), IL-8, IL-12, TNF-\(\alpha\), IL-1\(\beta\) and CD8 and with increased expression of endogenous IL-11. Studies for oprelvekin are ongoing.

**Strategy 4: Blockage of the activity of inflammatory cytokines**

Tumour necrosis factor-\(\alpha\) plays a critical role in the pathogenesis of psoriasis. Increased production of TNF-\(\alpha\) is seen in psoriasis and psoriatic arthritis that leads to chronic inflammation, tissue damage and hyperproliferation of keratinocytes. Tumour necrosis factor-\(\alpha\) is a pleiotropic, pro-inflammatory cytokine which is detected in eccrine sweat gland epithelium of normal skin and the epidermis and dermis of psoriatic skin lesions. It is released from T
cells, keratinocytes, dermal dendrocytes, macrophages and mast cells.34

The anti-TNF-α agent etanercept (Enbrel; Immunex Corporation, Seattle, WA, USA) is a recombinant human TNF-α receptor(p75) fused with the Fc portion of IgG1 that binds to the soluble and membrane-bound TNF-α (Fig. 4). Etanercept has demonstrated efficacy in the treatment of inflammatory diseases such as rheumatoid arthritis,35 juvenile rheumatoid arthritis, psoriatic arthritis36,37 and psoriasis.38–43 Etanercept is currently TGA-approved for moderate to severe chronic plaque psoriasis, rheumatoid arthritis, psoriatic arthritis and juvenile chronic arthritis in Australia.

Etanercept is administered subcutaneously. The recommended regimen is 50 mg twice weekly for the first 12 weeks and then 50 mg weekly thereafter. Dosing is continuous.

In a 24-week, placebo-controlled, double-blind, parallel-group, phase III study,39 patients with plaque psoriasis were randomized to receive placebo (n = 166) or etanercept subcutaneously at a low dose (25 mg once weekly, n = 160), a medium dose (25 mg twice weekly, n = 162), or a high dose (50 mg twice weekly, n = 164). After 12 weeks, patients in the placebo group began twice weekly treatment with 25 mg of etanercept. The primary measure of efficacy was the proportion of patients who achieved at least 75% improvement from baseline in the PASI score at week 12. There was such an improvement in 4% in the placebo group, 14% in the low-dose etanercept group, 54% in the medium-dose etanercept group and 49% in the high-dose etanercept group (P < 0.001 for all three comparisons to placebo). The mean percentage improvements in the PASI score from baseline were significant for all three etanercept groups as early as week 2 of the study. The clinical response of etanercept continued to improve with longer treatment. At week 24, there was at least a 75% improvement in the PASI score from baseline in 25% of patients in the low-dose group, 44% in the medium-dose group and 59% in the high-dose group. At week 12, the percentage of patients who were ‘clear’ or ‘almost clear’ in the PGA were 25% in the low-dose group, 54% in the medium-dose group and 49% in the high dose group as compared with 5% in the placebo group (P < 0.001 for all three comparisons to placebo). These differences were significant as early as week 4 and continued to improve with longer treatment. The mean percentage improvement from baseline in the DLQI was significant in all etanercept groups by week 2. By week 12, the mean improvement was 47.2% in the low-dose group, 50.8% in the medium-dose group and 61% in the high-dose group as compared with 10.9% in the placebo group (P < 0.001 for all three comparisons to placebo). The study demonstrated that etanercept produced significant dose-dependent improvements in the PASI score from baseline which were evident as early as week 2.

Of the 573 patients who completed 24 weeks of the initial blinded treatment, 157 (27.4%) failed to achieve at least a 50% improvement in their PASI scores from baseline. They entered a 12-week open-label extension and 42.1% (61 of the 145 incomplete responders, 12 dropouts) achieved at least a 50% improvement in their PASI scores from baseline and 11.7% (17 of the 145 incomplete responders) achieved at least a 75% improvement in their PASI score from baseline.40 This suggests that psoriasis patients who fail to achieve at least 50% improvement in PASI from baseline may continue to improve with further etanercept treatment and they may achieve a clinically meaningful response. Patients (at the end of week 24) who achieved at least 50% improvement in their PASI score from baseline discontinued etanercept and entered a drug withdrawal study period until their disease relapsed.43 The durability of treatment was defined as the time period from the discontinua-

![Figure 4](image-url)  
**Figure 4**  Activity of TNF-α is blocked by recombinant human TNF-α receptor fusion protein (etanercept) and chimeric antibody (infliximab). This illustration has been provided by Biogen Idec. TNF, tumour necrosis factor.
tion of etanercept (week 24) until the first visit at which at least 50% of PASI improvement that occurred between baseline and week 24 was lost. Seventy-one per cent (409 of the 575 patients who completed 24 weeks) entered the study withdrawal phase. The median time to disease relapse was 85 days, with 25% not relapsing until at least 141 days. The study showed that withdrawal from etanercept following a clinical response results in the return of signs and symptoms in a gradual manner with treatment response maintained for approximately 3 months.

Mild to moderate injection site reactions characterized by pain, swelling and erythema are the most frequent adverse effects associated with etanercept. Post-marketing studies have identified serious infections, sepsis and fatalities. Many of these infections occurred in those who were predisposed to infections because of an underlying immunosuppressive state brought on by previous immunosuppressive therapies. Rare cases of tuberculosis have been reported. Therefore, etanercept should not be administered to those with sepsis or active infections, including chronic and localized infections, and tuberculosis screening is mandatory before initiating etanercept. Eighteen cases of non-Hodgkin lymphoma occurring after the initiation of etanercept have been reported to the FDA between 1999 and 2000. However, patients with psoriasis and rheumatoid arthritis have an increased risk of lymphoma (Hodgkin and non-Hodgkin type) compared with the general population.

In post-marketing surveillance, rare cases of aplastic anaemia and central nervous system demyelinating disorders, transverse myelitis, optic neuritis and multiple sclerosis and new onset or exacerbation of seizure disorders have been reported. In those cases, a causal relationship to etanercept is not established. There may also be an increased risk of skin malignancies. A greater percentage (11%) of patients treated with etanercept developed a new positive ANA titre of 1:40 or greater compared with 5% of patients receiving placebo. Additionally, a greater percentage (15%) of patients treated with etanercept developed anti-dsDNA antibodies compared with 4% of patients receiving placebo. Drug-induced systemic lupus erythematosus and subacute cutaneous lupus erythematosus have been reported. Before therapy, patients should have baseline HIV (in high-risk groups) and hepatitis serology, tuberculin skin testing, full blood count, liver function and biochemical investigations.

In a case series of six patients, etanercept in combination with other systemic medications and topical medications demonstrated additional benefit to patients with severe recalcitrant psoriasis. All the six patients were treated with a variety of systemic agents and topical therapies: two received oral methotrexate 20 mg and 15 mg weekly, one received oral acitretin 25 mg on alternate days and oral hydroxyurea 1.5 g daily, one received oral acitretin 25 mg on alternate days and UVB (type not specified) weekly, one received oral cyclosporin 200 mg daily, and one received topical calcipotriene ointment. The PASI scores before etanercept treatment were 29, 24, 28, 14, 27 and 22, respectively. In each case, the disease activity showed marked improvement after the addition of etanercept therapy. The PASI scores after etanercept therapy were 10, 12, 10, 7, 14, and 10, respectively. No added toxicity was found. Psoriasis and psoriatic arthritis were successfully treated with etanercept and methotrexate in a patient unresponsive to infliximab. Methotrexate, 15 mg orally every week was combined with etanercept 25 mg administered subcutaneously twice every week. After 12 weeks, the patient’s psoriasis and psoriatic arthritis were completely resolved.

Infliximab (Remicade; Centocor Inc., Malvern, PA, USA) is a mouse/human chimeric antibody to TNF-α comprising a mouse variable region and a human IgG1-α constant region. Infliximab is able to bind to the soluble and transmembrane TNF-α molecules, thereby neutralizing the effects of TNF-α (Fig. 4). Infliximab is currently licensed in Australia and the USA for the treatment of fistulizing Crohn’s disease, rheumatoid arthritis and ankylosing spondylitis. Infliximab is also being investigated for the treatment of hidradenitis suppurativa and Sjögren’s disease.

Infliximab is administered intravenously at a dose of 5 mg/kg over 2 hours at weeks 0, 2 and 6. Subsequent infusions may be given every 8 weeks at a dose of 5 mg/kg. Recent case reports have demonstrated the effectiveness of infliximab with marked improvement in psoriasis as demonstrated by the PASI score.

In a randomized controlled trial, the response to infliximab was similar to cyclosporin in terms of the high proportion of patients achieving clearance and the rapidity of clearance. Thirty-three patients with moderate to severe psoriasis were randomized to intravenous placebo (n = 11), infliximab 5 mg/kg (n = 11) or infliximab 10 mg/kg (n = 11) at weeks 0, 2 and 6. The PGA at week 10 was the defined primary efficacy end-point. Nine of 11 (82%) patients in the infliximab 5 mg/kg group and 10 of 11 (91%) patients in the infliximab 10 mg/kg group achieved the primary end-point of a good, excellent, or clear rating on the PGA, compared with only two of 11 (18%) patients in the placebo group. The change in PASI was a secondary end-point. Nine of 11 (82%) patients in the infliximab 5 mg/kg group and eight of 11 (75%) patients in the infliximab 10 mg/kg group had at least 75% improvement in the PASI score from baseline, compared with two of 11 (18%) patients in the placebo group. The mean percentage PASI score improvements from baseline were significantly higher among those who received infliximab as early as week 2. The median time to response was 4 weeks. This demonstrates that one of the advantages of infliximab is that it is able to provide a rapid response.

Infliximab provides a sustainable effect through week 26 as demonstrated in an open-label extension study from that above. Non-responders in the placebo group were assigned (1:1) to receive open-label 5 or 10 mg/kg of infliximab at weeks 10, 12 and 16. Responders in the placebo group were followed up for relapse (loss of 50% or more of improvement attained in the PASI at week 10) and then offered infliximab in the same manner as the non-responders in the placebo group. Non-responders in the 5 mg/kg group were offered a single infusion of 10 mg/kg
of infliximab and followed up for response, whereas non-
responders in the 10 mg/kg were discontinued from the
study. Those who responded to treatment with 5 or 10 mg/kg
in the first part of the study were followed up for relapse
and offered single-dose infusions of infliximab on relapse
(loss of at least half of the improvement in PASI scores
achieved at week 10). Among all patients treated with
infliximab, 57% (17 of 30) maintained at least 50% improvement in their PASI score from baseline and 50% (15 of 50) maintained at least 75% PASI improvement at
week 26. For those who received 5 mg/kg of infliximab,
40% maintained at least a 50% improvement and 35% main-
tained at least a 75% improvement from baseline
through week 26. For those who received 10 mg/kg of
infliximab, 75% maintained at least a 50% improvement and 67%
maintained at least a 75% improvement from baseline
through week 26. The study demonstrated that
infliximab produces a rapid, effective and sustainable
effect and may be used as an infrequent dosing regimen.

Alternatively, a maintenance dose of every 8 weeks
rather than infrequent dosing may be considered after the
initial week 0, 2 and 6 induction regimen. This was shown in
a double-blind, placebo-controlled trial comprising a 3-
dose induction regimen followed by a further single infu-
sion at week 26. Eligible patients were randomized in a
1:2:2 ratio to intravenous infusions of placebo (n = 51),
infliximab (5 mg/kg, n = 99) or infliximab (5 mg/kg, n = 99)
and were treated at weeks 0, 2 and 6. At week 26, patients
with a PGA of moderate to severe disease activity were
eligible for a single additional intravenous infusion.
At week 10, 72% (71/99) of patients treated with infliximab
(5 mg/kg) and 88% (87/99) of patients treated with inflix-
imab (5 mg/kg) achieved a PASI-75 compared with 6%
(5/51) of patients treated with placebo (P < 0.001). At week
10, 84% (85/99) of patients treated with infliximab (5 mg/kg)
and 97% (96/99) of patients treated with infliximab
(5 mg/kg) achieved a PASI-50 compared with 22% (11/51)
of patients treated with placebo (P < 0.001). The response
was evident after the first infusion and at week 2, 54% and
40% of patients in the 5 mg/kg and 5 mg/kg infliximab
treatment groups, respectively, already achieved PASI-50
compared with 4% of patients in the placebo group
(P < 0.001). By week 4, 55% and 47% of patients in the
5 mg/kg and 5 mg/kg infliximab treatment groups, respec-
tively, achieved PASI-75 compared with no patients in the
placebo group (P < 0.001). Patients in the 5 mg/kg and
5 mg/kg groups began to lose response after week 10 and
week 14, respectively. This suggests that a regimen of
maintenance dosing every 8 weeks should be considered
for patients. Four weeks after re-treatment at week 26,
58%, 64% and 18% of patients who were re-treated in the
5 mg/kg, 5 mg/kg and placebo groups, respectively,
achieved a PGA of mild, minimal or clear.

The efficacy of infliximab has also been demonstrated in
improvements in the DLQI. Patients who receive a dose of
5 mg/kg at weeks 0, 2 and 6 can expect an improvement in the
DLQI of 61% as early as week 2. By week 10, patients
can expect an improvement in the DLQI of 91%. The

The most commonly reported adverse events from trials
include infusion-related reactions (dyspnoea, urticaria,
hypotension, flushing and headache). Antibodies produced
by the patient to infliximab may potentially neutralize the
drug and block its effect, leading to dose escalation. Meth-
otrexate may be co-administered with infliximab to prevent
the development of neutralizing antibodies. Erythema
multiforme and a lichenoid eruption have been reported.
Pulmonary tuberculosis may be reactivated by treatment
with infliximab, hence patients should be screened for
tuberculosis before infliximab treatment. Infliximab is
contraindicated in patients with moderate to severe conges-
tive heart failure (New York Heart Association class III/IV)
because of infliximab-related reactions of hypotension and
dyspnoea. Eight cases of non-Hodgkin lymphoma occur-
ing after the initiation of infliximab have been reported to
the FDA between 1999 and 2000.

Three patients have been reported using infliximab in
combination with other immunosuppressants. The first
two patients received cyclosporin (100–150 mg daily) and
infliximab at weeks 0, 2 and 6, and the third patient
received intramuscular methotrexate 25 mg weekly and
narrowband UVB once weekly and infliximab at weeks 0, 2
and 6. The first patient’s skin had a significant but not
complete improvement at week 8. The second patient’s
skin was completely clear at week 4; however, she suffered
a relapse on her hands and feet at week 15. The third
patient’s skin was completely clear by week 7 and she
enjoyed prolonged remission of 50 weeks post initial infu-
sion. In another case report, the beneficial effects of the
combination of infliximab with oral methotrexate in
the treatment of severe psoriasis was demonstrated. The
patient’s baseline PASI score was 27.2 and he received a
single does of infliximab intravenously while he continued
methotrexate 20 mg weekly and emollients. Improvement
in his skin was noted within 5 days of the infusion when his
PASI score had reduced to 15.2, and 5 weeks post infusion
his PASI score was 4.1. Eight weeks post infusion his psori-
asis was still clear.

Adalimumab (Humira; Abbott Laboratories, Abbott Park,
II., USA) is the first fully human anti-TNF-α monoclonal
antibody. It binds specifically to soluble and membrane-
bound TNF-α and blocks its interaction with the p55 and
p75 cell surface TNF receptors. It is currently approved in
the USA for rheumatoid arthritis.

A case report of two patients with long-standing psoriasis
both responded to adalimumab after multiple treatment
failures with conventional and experimental antipsoriatic
medications. The first patient received fortnightly subcu-
taneous injections of adalimumab 40 mg. The PASI score
after the first 8 weeks (three injections) was 46.5 and
improved to 12 after six injections (12 weeks following
commencement of therapy). At 20 weeks after commence-
ment of therapy, her PASI score was 5.7 and after 40 weeks
her disease remains quiescent with a PASI score of 2.2. The
second patient also received fortnightly subcutaneous
injections of adalimumab 40 mg, at which time his psoriasis
involved approximately 50% of his body surface area with
a PASI score of greater than 18. His PASI score was 5 at

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16 weeks after the initial dose and after 6 months of therapy, his PASI score was less than 5. This improvement continues to be maintained at 18 months post treatment. Both patients tolerated adalimumab with no adverse events reported.

From the clinical trials for rheumatoid arthritis, the most common adverse events reported were headache, injection site pain and nausea. Adalimumab is currently undergoing clinical trials for psoriasis and psoriatic arthritides.

**OTHER BIOLOGIC AGENTS IN EXPERIMENTAL PHASE**

Table 2 outlines those biologics that are on or close to market and are approved by the FDA or TGA for psoriasis and other indications. Recently, alefacept, efalizumab and etanercept have been approved by the TGA in Australia for the treatment of moderate to severe psoriasis in adults. Efalizumab and etanercept are now listed as part of the Pharmaceutical Benefits Scheme in Australia, but only for PASI > 15. Other biologics for psoriasis that are still in the early phase of clinical trial development are listed in Table 3. Readers are referred to the provided references for further discussion.

**CONCLUSION**

Systemic therapies for the treatment of psoriasis up until now have been limited by their safety profile. New advances in genetic engineering have led to the exciting development of biologic therapies which have demonstrated a safer approach to the treatment of psoriasis and hold significant promise for those who are severely debilitated by this disease.

There is obvious potential for the use of biologic agents in combination with existing therapies. Such an approach may be synergistic and may offer the advantage of minimizing the side-effects of other systemic therapies in the treatment of patients with psoriasis. Combinations of biologic agents with one another, with other systemic immunosuppressive therapies, with topical treatments, or with phototherapy open the door to a world where control of psoriasis, more prolonged remission and improved psychosocial well-being may be achieved.

**ACKNOWLEDGEMENT**

The authors would like to acknowledge Biogen Idec (Figs 1,3 and 4) and Serono (Fig. 2) for providing the illustrations.

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Trade name</th>
<th>FDA-approved indication</th>
<th>TGA-approved indication</th>
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<tbody>
<tr>
<td>Alefacept</td>
<td>Amevive</td>
<td>Chronic plaque psoriasis: moderate to severe</td>
<td>Chronic plaque psoriasis: moderate to severe</td>
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<tr>
<td>Efalizumab</td>
<td>Raptiva</td>
<td>Chronic plaque psoriasis: moderate to severe</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td>Psoriatic arthritis</td>
<td>Psoriatic arthritis</td>
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<tr>
<td></td>
<td></td>
<td>Ankylosing spondylitis</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>Chronic plaque psoriasis: moderate to severe</td>
<td>Chronic plaque psoriasis: moderate to severe</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid arthritis</td>
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**Table 3**

<table>
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<tr>
<th>Biologic</th>
<th>Action</th>
<th>Reference</th>
<th>Status</th>
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<tbody>
<tr>
<td>Denileukin dfitox, DABm,IL-2 (Ontak; Ligand Pharmaceuticals, San Diego, CA, USA)</td>
<td>A fusion protein consisting of IL-2 and a portion of the diphtheria toxin molecule. Denileukin dfitox is specifically toxic to T-lymphocytes bearing high affinity IL-2 receptors.</td>
<td>76</td>
<td>Approved for cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>HuMax-CD4 (Genmab A/S, Copenhagen, Denmark)</td>
<td>A fully human monoclonal anti-CD4 antibody. Induces a dose-dependent reduction in the CD4 cell count, with reduction primarily in the memory T-cell subset with only a minor decrease in the native T-cell subset.</td>
<td>77</td>
<td>Ongoing phase II study</td>
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</tbody>
</table>

COD, cluster of differentiation; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; K16, keratin 16; Th, T-helper; TNF, tumour necrosis factor.
REFERENCES


6. Sanders ME, Makgoba MW, Sharrow SO, Stephany D, Springer TA, Young HA, Shaw S. Human memory T lymphocytes express increased levels of three adhesion molecules (LFA-5, CD2 and LFA-1) and three other molecules (UCHL 1, CDw29, and Pgp-1) and have enhanced IFN-γ production. J. Immunol. 1988; 140: 1401-7.


PROFESSIONAL DEVELOPMENT PROGRAM

Select the most correct answers – multiple answers possible for questions 1–11

1. Biologic response modifiers:
   a. Include immunoreactive compounds
   b. Include hormones
   c. Include neuroactive compounds
   d. May be derived from human and animal sources
   e. May be derived from plant material

2. Concerning the generic names for biologic agents:
   a. Receptor–antibody fusion proteins have the suffix – cept
   b. Humanized monoclonal antibodies have the prefix – ximab
   c. Human monoclonal antibodies have the suffix – ximab
   d. Chimeric monoclonal antibodies have the suffix – zimab
   e. Chimeric monoclonal antibodies have the suffix – zimab

3. Regarding fusion proteins:
   a. Fusion proteins consist of a human receptor domain that allows solubility in plasma
   b. The constant portion of immunoglobulin G allows solubility in plasma
   c. Alefacept is a fusion protein combining two binding sites of human TNF-α with the hinge, CH2 and CH3 sequences of G1
   d. Currently marketed fusion proteins are available for oral administration
   e. The use of fusion proteins is well studied in pregnant women

4. Strategies for immunomodulation therapy for psoriasis include:
   a. Stimulation of T helper cell activation
   b. Reduction of the number of pathogenic T cells
   c. Inhibition of T-cell migration
   d. Stimulation of inflammatory cytokines
   e. Inhibition of interleukin 15 release from B cells

5. Concerning alefacept:
   a. Onset of clinical effect in psoriasis is slow
   b. Trials have shown transient decreases in CD45RO+ memory T cells
   c. Monitoring CD8+ T lymphocyte at baseline and fortnightly for four consecutive weeks
   d. Therapy should be ceased if the CD8+ T lymphocyte count remains below 250 cells/μl for four consecutive weeks
   e. May have the potential to induce long-term remission

6. Etanercept can interfere with the development of psoriatic plaques by:
   a. Binding to soluble and membrane bound TNF-α
   b. Blocking T-cell migration into the skin
   c. Inhibiting T-cell activation
   d. Modulating the immune system to a type-2 cytokine pattern
   e. Stimulating interleukin 15 release from B cells

7. Concerning efalizumab:
   a. Is a humanized form of a porcine antibody targeted against CD11a
   b. Can be administered orally
   c. Fever, nausea, vomiting, headaches, chills, asthenia myalgia and pharyngitis are included in the most frequent adverse events reported in clinical trials
   d. The adverse events are most frequently reported after the third dose
   e. Symptomatic improvement in itch is not shown in phase III studies

8. Etanercept:
   a. Is a human receptor-antibody fusion protein
   b. Is released from T cells, dermal dendrocytes and macrophages
   c. Is a recombinant murine TNF-α receptor fused with the Fc portion of IgG1
   d. Binds to soluble and membrane bound TNF-α
   e. Causes increased serum levels of free TNF-α by blocking the receptor

9. Etanercept post-marketing studies have reported:
   a. Tuberculosis
   b. Central nervous system demyelination disorders including transverse myelitis, optic neuritis and multiple sclerosis
   c. Frequent cases of aplastic anaemia
   d. Anti-dsDNA antibodies more frequently than in the placebo patients but no cases of drug-induced systemic lupus erythematosus
   e. New onset or exacerbation of seizure disorders

10. Infliximab:
   a. Is the only biologic agent studied widely in lactating women
   b. Is approved by the FDA and TGA for use in palmoplantar pustular psoriasis
   c. Binds to soluble and transmembrane TNF-α molecules
   d. Has a rapid, effective and sustainable effect on PASI scores
   e. May induce antibodies that neutralize the agent and block its effect

11. Recommended dosing regimens for treatment of chronic plaque psoriasis include:
   a. Alefacept is continuous dosing as weekly subcutaneous injections
   b. Efalizumab is administered as a weekly intravenous infusion
   c. Adalimumab is given as an ongoing weekly intramuscular injection
   d. Infliximab is used as an intravenous infusion at weeks 0, 2 and 6 then every 8 weeks
   e. Etanercept is administered as a subcutaneous injection once or twice each week

Directions for questions 12–23: For each numbered item, choose the appropriate lettered item. There is only one correct answer, but the same letter can be chosen more than once in any one question.

With respect to questions 12–15:
   a. Etanercept
   b. Infliximab
   c. Efalizumab
   d. Adalimumab
   e. Infliximab

12. Is a mouse/human chimeric antibody to TNF-α
13. Is a fully human anti TNF-α monoclonal antibody
14. Is a recombinant human TNF-α receptor fused with the Fc portion of IgG1
15. Is a humanized antibody directed against CD11a

With respect to questions 16–19:
   a. Efalizumab
   b. Adalimumab
   c. Infliximab
   d. Etanercept

16. Crohn’s disease is a TGA approved indication
17. Ankylosing spondylitis is a TGA approved indication
18. Psoriatic arthritis is a TGA approved indication
19. Rheumatoid arthritis is the only FDA approved indication currently

With respect to questions 20–23:
   a. Efalizumab
   b. Infliximab
   c. Alefacept
   d. Etanercept

20. Treatment has been associated with thrombocytopenia
21. Subcutaneous injections have been associated with serious infection, including tuberculosis, sepsis and fatalities
22. Treatment is contraindicated in patients with moderate to severe congestive heart failure due to infusion related reactions of hypotension and dyspnoea
23. Weekly intramuscular injections for 12 weeks has the potential for long-term remission

Answers to PDP questions from Vol. 47, No. 5:
1. a,d  6. a,c,d  11. a,b,e  16. b  21. c
2. a,d,e  7. a,b,d  12. d  17. c  22. a
3. b,c,d,e  8. a,b,e  15. c  18. a  25. d
4. a,b,c,e  9. b,d,e  14. a  19. d
5. b,c,e  10. b,d  15. b  20. b

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Professional Development Program
Category B

*Australasian Journal of Dermatology*
Volume 47, No. 4, 2006

Name: ................................................................. PDP No.: ..............

State: .................................................................

Questions 1–11
Circle the most appropriate answers — multiple answers possible. Each question must have all correct answers circled in order to receive points.

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Questions 12–25
Circle the correct answer.

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Pass Mark: 75% (if you obtain this mark or higher you will be granted 1.5 hours Category B PDP credit).

If you feel the need to indicate ambiguity in a question, please do not write comments on the answer sheet.

Please return your answer sheet to College by 1 January 2007. Answer sheets received after this date will not be accepted.