Biological treatments for psoriasis

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Psoriasis is a chronic disease with significant morbidity and particularly severe effects on a patient’s quality of life. Topical treatments are usually effective in cases of limited psoriasis. Patients with severe disease require systemic medicines or ultraviolet light treatment in order to obtain symptomatic relief. Until recently, the available systemic medicines have been immunological agents such as cyclosporin, methotrexate, hydroxy carbamide, fumaric acid esters, ultraviolet light treatment with or without psoralens and antiproliferative agents such as retinoids. All of these treatments are associated with side effects, the severity of which increases with increasing duration of use. There has always been a lack of highly effective treatment. There has recently been expansion in the knowledge of the role of the immune system and in particular T cells in the pathogenesis of psoriasis. This has led to development of selective immunologically directed treatments for the psoriasis widely known as ‘biologics’. This article will review the currently used biological treatments for psoriasis. Alefacept, efaluzumab, infliximab and etanercept are all biologicals that have been in use in recent years in the treatment of psoriasis, and have gained EU and/or US approval. The immunopathogenesis of psoriasis, mechanism of action of the biologicals and the overall efficacy and side effects of individual drugs will be discussed herein.

Psoriasis is a chronic disease affecting approximately 2% of the US and European population [1]. The disease incidence varies in different parts of the world with the lowest incidence found near the equator and with increasing frequency towards the poles. Northern European Caucasians appear to be affected most frequently, followed by Asian and African populations and the disease is least common in natives of North and South America [2]. The incidence is equal in men and women. It has been estimated that psoriasis affects approximately 4.55 million people over the age of 18 years in the USA, approximately a million of which have substantial dissatisfaction with their treatment [3]. Psoriasis may appear at any age but typically has a bimodal onset with the first peak between 16–22 and the second between 57–60 years of age [4,5].

Psoriasis is usually diagnosed clinically. The prevalence of psoriatic arthritis in patients with psoriasis ranges from between 6–39% [6]. Psoriasis can cause physical and mental disability comparable with that of other major medical illnesses, such as heart disease, hypertension, depression and rheumatoid arthritis [7,8]. Approximately a quarter of all patients with psoriasis require systemic therapy, phototherapy or both to keep the disease under control [9]. Commonly used systemic therapies for psoriasis include cyclosporine, methotrexate (MTX), oral retinoids and psoralen plus ultraviolet light (PUVA) [10] and fumaric acid esters (in Germany) in addition to a recently increasingly use of narrowband UVB. However, none of the currently available therapies have a favorable long-term outcome due to a lack of consistent efficacy over time [11] in addition to the inconvenience and serious toxicity associated with their long-term use [12].

Immunopathogenesis of psoriasis & mechanism of action of biological drugs in psoriasis

Psoriasis is characterized clinically and histologically by increased proliferation of the epidermal cells associated with shortening of the epidermal cell cycle and abnormal keratinocyte maturation. Psoriasis was initially considered to be a disorder of keratinocytes but it is now known that infiltration by T cells causes keratinocyte hyperproliferation [13]. There is an associated inflammatory cell infiltrate of neutrophils and CD4+ T-lymphocytes in the dermis and CD8+ T-lymphocytes in the epidermis in addition to activated Langerhans’ cells, macrophages and dermal dendritic cells (DCs) in the
psoriatic plaques [14]. Although the precise nature of the events which cause proliferation of the epidermis by interaction between inflammatory cells and epidermal cells is not entirely clear, there has been increasing evidence that activated T cells and the cytokines play an important role in the pathogenesis of psoriasis [15]. T cells are divided into two phenotypes, based on the nature of the cytokines they produce. T-helper (Th) type 1 cells and cytotoxic T cells (Tc1) produce interleukin (IL)-2, tumor necrosis factor (TNF)-α, interferon (IFN)-γ and IL-8, which mediate cell-mediated immunity and T-cell cytotoxicity. Th2 and Tc2 cells produce IL-4, IL-5 and IL-13 and they mediate allergic and mucosal responses. Cytokines produced by each type of cell tend to inhibit the function of the other cell type [14]. The T-cell-directed immune response in psoriasis is primarily of type 1, since psoriatic skin has increased TNF-α and IFN-γ levels compared with nonlesional skin [14,16] and therefore there is a higher ratio of IFN-γ to IL-4 in circulating T cells in psoriasis [14,17]. IFN-γ secreted by Th1 cells stimulates macrophages to secret other inflammatory cytokines including TNF-α [18,19]. It has been shown that levels of Th2 cytokines, such as IL-10, are low in psoriasis [20].

Newer treatments for psoriasis are being developed to more specifically target these immunological events and thereby produce fewer side effects. These newer agents are proteins known as immunobiologics or ‘biologics’, and include recombinant cytokines, monoclonal antibodies (mAbs) and fusion proteins. Their targets are extracellular and include adhesion proteins, receptors, cytokines and chemokines. The role of T cells in the process of the formation and continuation of the psoriatic plaque can be explained by following three simple steps. The mechanism of action of individual biologic agents and the role of TNF-α are also discussed in relation to these relevant steps.

**T-cell activation**

Antigen-presenting cells (APCs) (Langerhans' cells in the skin) activate T cells. On exposure to antigens, which are unknown in psoriasis, APCs mature and express the processed antigen, either with major histocompatibility complex type I or II, and then migrate to local lymphatic tissues. Antigen recognition by the T cell occurs due to an interaction between the major human leukocyte antigen (HLA) I or II antigen complex on the APC and T-cell receptor. The adhesion molecules’ leukocyte function-associated antigen (LFA)-1 of the T cell binds to the intracellular adhesion molecule (ICAM) on the APC and its two subunits (CD11a and CD18) in addition to CD2 on the T cell, bind to LFA-3 on the APC [18,19,21,22]. These molecules stabilize the synapse between the T cell and the APC and provide costimulation of antigen recognition. The HLA-I–antigen complex binds to the CD8+ cytotoxic T cell and the HLA-II–antigen complex binds to the CD4+ Th cell [18,21]. Finally, binding of CD28+ on the T cell to CD80+ and CD86+ on the APC completes T cell stimulation. The synergistic binding of the T-cell receptor and CD28 is necessary for promoting release of the cytokines IFN-γ, IFN-α and IL-2 [20]. In the presence of IL-12, T cells differentiate into Th1 cells, which undergo activation and clonal proliferation through IL-2 secretion and binding on its own surface [21,23]. Cytotoxic CD8+ T-lymphocyte function is augmented by binding of CD2+, which is present on all T-lymphocyte subgroups to LFA-3 on the APCs [22–26]. Activated T cells need to reach the skin to take part in the pathogenesis of psoriasis and thus the next step follows.

Alefacept acts by binding to CD2 on T cells (Figure 1), thus preventing initial binding of T cells with APCs as well as augmentation of cytotoxic CD8+ T-lymphocyte function. In addition, natural killer cells bind the immunoglobulin (Ig)G1 portion, causing T-cell apoptosis [27].

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**Figure 1. T cell activation by interaction with APC.**

APC: Antigen-presenting cell; CD: Cluster of differentiation; HLA: Human leukocyte antigen; ICAM: Intracellular adhesion molecule; LFA: Leukocyte function-associated antigen.
Memory T cells are more selectively depleted due to a higher expression of CD2. It is for this reason that T-cell counts have to be frequently monitored during therapy.

** Trafficking of activated T cells into the skin **

After initial clonal proliferation of T cells in the lymph node, a minority then express CD45RO and become memory cells, while the majority undergo apoptosis. These memory T cells leave the lymph nodes, circulate in the blood and then migrate into the skin to produce lesions of the psoriasis [13].

To enter the skin, T cells must attach to endothelial cells in the capillaries through adhesion molecules, and it is known that ICAM-1 and E-selectin are upregulated on endothelial cells in cutaneous inflammation [27,29]. The activated T cells expresses cutaneous lymphocyte antigen (CLA) and LFA-1, which binds to E-selectin and ICAM-1 respectively, on the endothelial cells [30,31]. Once this adhesion occurs, T cells flatten and migrate through the endothelium in a process known as diapedesis. The proinflammatory cytokine, IL-8, plays an important role in trafficking both neutrophils and lymphocytes in lesions of psoriasis [32]. Efalizumab binds to CD11α, the α subunit of LFA-1, and inhibits T-cell activation, T-cell trafficking and extravasation by blocking its interaction with ICAM-1 [33] (Figure 1 & 2).

The predominant subclass of T-lymphocytes is the CD4+ helper in the dermis and CD8+ cytotoxic in the epidermis, and although the specific antigen is not known, these cells undergo oligoclonal expansion in psoriatic lesions [34]. Chemokine production is enhanced from endothelial cells and keratinocytes by TNF-α and IFN-γ, which in turn play an important role in the migration of the CD8+ T-lymphocytes in the epidermis, attracting more T cells in the skin and augmenting inflammation in the psoriasis lesion [13,30–32,35,36].

** The positive feedback cycle of continuous T-cell activation in the skin & the role of TNF-α **

T cells play a central role in causing keratinocyte changes of psoriasis by producing cytokines which induce other cells, such as epidermal keratinocytes, macrophages, and DCs, to secrete their own cytokines. These cytokines maintain the positive feedback loop in the skin by stimulating the cells involved in their production, thereby sustaining the chronic psoriasis plaque [13,14].

IFN-γ produced by Th1 T cells causes augmentation of keratinocytes, proliferation and differentiation, stimulates macrophages to release TNF-α, induces ICAM, VCAM and E-selectin and inhibits IL-4 (and Th2 expression). TNF-α facilitates differentiation of T cells to type 1 cells and induces ICAM, VCAM and E-selectin. Vascular endothelial growth factor, which is released by T cells, is likely to be responsible for vascular growth and remodelling [13,35]. TNF-α stimulates IFN-γ which in turn induces TNF-α in a positive feedback loop amenable to biological therapies that target TNF-α [13]. IL-2 produced by type 1 T cells induces clonal proliferation of Th1 cells and activates macrophages, while IL-12 produced by APCs encourages Th1 differentiation [35].

It is clear from the above discussion that TNF-α plays an important role in the pathogenesis of psoriasis and so inhibition of TNF-α can improve psoriasis. Etanercept, infliximab and adalimumab are effective in the treatment of psoriasis as a result of their anti-TNF-α activity. Etanercept and efalizumab interfere with the actions of TNF-α in a number of different ways. Etanercept is a soluble fusion protein which takes the form of a TNF-α receptor. It binds irreversibly to soluble TNF-α reducing TNF-α available for signalling thus modulating the biological responses regulated by TNF-α [37]. Infliximab, however, is a chimeric mouse–human mAb of TNF-α which binds to soluble and transmembrane forms of TNF-α, and thereby inhibits TNF-α activities. It binds with a higher affinity and can induce apoptosis of cells expressing TNF-α on their surface. This makes it more potent and inhibits granuloma formation with implications for infection risks [38]. Adalimumab is a monoclonal anti-TNF-α antibody similar to infliximab, but is fully humanized. It blocks the interaction of TNF-α with P55 and P75 subunits of the TNF-α receptors and modulates biological responses regulated by TNF-α [39] (Figure 2).

** Biological treatments **

The efficacy, long-term treatment, side effects, pretreatment screening and monitoring, the role of antibodies against biologics and choice of biologic agent for psoriasis are described below based on published trials and drug information provided by the manufacturing companies.

** Alefacept **

** Efficacy **

Ellis and Krueger used intravenous alefacept (0.025, 0.075, or 0.150 mg/kg of body weight) or placebo every week in 229 patients in a
multicenter, randomized, placebo-controlled, double-blind study [40]. Mean psoriasis area severity index (PASI) scores were between 14 and 20 in all groups before starting treatment. The mean reduction in PASI score 2 weeks after treatment was greater in the alefacept groups (38, 3 and 53% in the groups receiving 0.025, 0.075 and 0.150 mg/kg respectively) than in the placebo group (21%, p > 0.001). The proportion of patients with improvements of greater than 50 or 75% of the PASI score (PASI 50, 75) at 2 and 12 weeks of treatment were significantly higher in the three alefacept groups than placebo.

A multicenter, Phase III study of alefacept was based on two treatment courses, each with a 12-week treatment and 12-week follow-up period. A total of 553 patients were randomized in three cohorts for once-weekly 7.5 mg intravenous alefacept or placebo. Cohort 1 received alefacept during both courses, cohort 2 received alefacept followed by placebo and cohort 3 received placebo followed by alefacept [41]. During the first course of treatment, the number of patients achieving PASI 50 (56%) and PASI 75 (28%) were significantly greater in the alefacept-treated cohorts than placebo (24 and 8% respectively; p > 0.001 for both). In addition, patients who were randomized...
Biological treatments for psoriasis – REVIEW

to receive two courses of alefacept showed more benefit at the end of the second course compared with the end of the first course (64 and 37% of patients showed benefits in PASI 50 and 75, respectively, as compared with 49 and 19%, respectively, for placebo). Repeated courses of alefacept are known to be at least as effective and as well tolerated as the first course [42].

Another randomized, double-blind, placebo-controlled Phase III trial investigated the efficacy of intramuscular alefacept by randomizing a total of 507 patients in three groups [43] involving alefacept 10 mg, 15 mg or placebo once-weekly for 12 weeks followed by 12 weeks of observation. The number of patients achieving 75% or greater improvement in PASI 2 weeks after the study was greater in the alefacept-treated group than placebo. A total of 71% of patients who were treated with 15-mg alefacept maintained the improvement in their PASI during the 12-week follow-up period. These results are less favorable than with other biologics. The Dermatology Life Quality index (DLQI) and Dermatology Quality of Life Scales (DQoLS) were significantly improved in patients treated with Alefacept as compared to placebo, and the improvement correlates with improvement in PASI [44,45].

**Long-term efficacy & treatment**

It has been demonstrated, again by Krueger and Ellis, that in patients who were 'clear' or 'completely clear' in the above Phase II trial, 15% of the subjects had sustained benefit for a median of 10 months and up to 18 months without the need for retreatment [46]. A recent integrated analysis of 13 trials supports the safety and tolerability of Alefacept over a 5-year period [27]. The drug has not been used for long enough in a sufficient number of patients to know exactly the long-term benefits and side effects.

**Side effects**

The most common adverse reactions observed during alefacept therapy include pharyngitis, dizziness, increased cough, nausea, pruritus, myalgia, chills, injection-site inflammation, and accidental injury with a 2% higher incidence than the placebo group and chills with a 5% higher incidence [46].

The most serious adverse reactions observed during the clinical trials were lymphopenia (CD4+ count monitoring required), malignancies (lymphomas and squamous cell cancers of the skin), serious infections requiring hospitalization and hypersensitivity reactions.

**Efalizumab**

**Efficacy**

A Phase II multicenter, double-blind, placebo-controlled study enrolled 145 patients with PASI scores of 12 and above and evaluated efalizumab at either 0.1 (n = 22) or 0.3 mg/kg (n = 75) intravenously for 8 weeks compared with placebo (n = 48) [47]. Results demonstrated a greater than 50% reduction of psoriatic plaques in 48% of patients compared with 15% in the placebo group. Of the subjects in the 0.3 mg/kg-treated group, 25% achieved a 75% improvement in the Physicians Global Assessment versus 2% in the placebo group, and the adverse effects were minimal with flu-like symptoms most commonly reported.

This Phase III, multicenter, randomized, placebo-controlled, double-blind study [48] used efalizumab in 597 subjects. Efalizumab was administered at 1 or 2 mg/kg of body weight/week, or placebo, for 12 weeks, followed by either placebo or efalizumab for a further 12 weeks, depending on the response (subjects with 50% or more improvement in PASI at week 12 were randomized to continue on 2 mg/kg efalizumab every week, every other week or placebo). Efalizumab-treated patients had a statistically greater improvement as early as 4 weeks compared with placebo, and at the end of 12 weeks, 22 and 28% of subjects who received 1 and 2 mg/kg efalizumab respectively, showed a PASI 75 compared with 5% in the placebo group. The PASI 75 was maintained in 77% of the subjects at week 24 who continued to receive efalizumab as compared to 20% who were switched to placebo at the end of 12 weeks. It took 84 days for relapse (loss of at least 50% of the improvement in PASI) of psoriasis among subjects who had at least a 50% improvement in PASI at week 24.

In another Phase III, double-blind trial, 498 patients were randomized to receive subcutaneous efalizumab 1 or 2 mg/kg/wk (328/498) or placebo (170/498) for 12 weeks. At week 12, PASI 75 was achieved in 39 and 27% of efalizumab-treated patients (1 and 2 mg/kg, respectively) as compared with 2% in the placebo group (statistically significant) [49]. Subjects who failed to achieve PASI 75 at the end of 12 weeks (183) were rerandomized to placebo (60/183) or subcutaneous 1 (57/183) or 2 mg/kg/wk (60/183) efalizumab for another 12-week period. PASI-75 was achieved in an additional 20% of efalizumab-treated patients compared with 7% in the placebo group at week 24, and there was no significant change in the safety profile.
This Phase III, randomized, double-blind, parallel-group, placebo-controlled, 12-week study, followed by a 12-week open-label study, assessed the safety and efficacy of efalizumab for 24 weeks [50]. Initially, 556 patients were randomized to receive 1mg/kg of subcutaneous efalizumab weekly, or placebo, for the initial 12 weeks and 516 of these patients continued on subcutaneous efalizumab 1 mg/kg/week for a further 12 weeks. PASI 50 and 75 was achieved by 58.5 and 26.6% of the patients at week 12 and by 66.6 and 43.8% at week 24. The improvement in quality of life (QoL) measures at week 12 was maintained without cumulative toxic effects at week 24.

Long-term efficacy & treatment
PASI 50 was maintained in 30% of subjects during the 12 week follow-up after discontinuation of efalizumab [47]. A total of 47% of patients achieved PASI 75 at week 27 in this 36-month, extended-treatment trial of efalizumab. This 36-month continuous therapy trial involved 339 patients for the initial 12 weeks followed by maintenance treatment in 290 patients for a further 24 weeks. PASI 75 was achieved in 41% of patients at week 12 and by 47% of patients by week 27. The safety profile was sustained throughout 27 months [51].

Side effects
Although limited data are available to properly assess the risk of serious infection or malignancy, it does not appear to be higher in efalizumab-treated patients [48,37]. Overall, efalizumab appears to be well tolerated from a limited, combined-safety database of all studies involving 2762 patients [37].

The most common adverse event reported was flu-like symptoms, usually resolving after the first month of treatment. Thrombocytopenia is infrequent (0.3%), but important side-effect and platelet counts should be monitored during treatment [37]. Worsening of psoriasis has been reported in 0.7% of patients (5 out of 2589) during or after discontinuation of the treatment.

TNF-α inhibitors
Etanercept
Efficacy
Mease and colleagues reported a 75% improvement in PASI in 26% of patients and 46% improvement in median PASI at the end of 12 weeks as compared with a 0 and 9% improvement in the placebo-treated subjects, respectively, in a double-blind, randomized, placebo-controlled study [52]. They authors used twice-weekly subcutaneous etanercept for 12 weeks and also noted a benefit in 87% of patients with psoriatic arthritis who met the Psoriasis Arthritis Response Criteria (PsARC).

This 24-week, Phase III, double-blind, multicenter, placebo-controlled study [53] randomized 672 patients, 652 of which received either placebo or low-dose (25 mg/week), medium-dose (25 mg twice-weekly), or high-dose (50 mg twice-weekly) etanercept subcutaneously. After 12 weeks, patients in the placebo group received twice-weekly 25 mg etanercept subcutaneously for 12 weeks. At the end of the 12 weeks there was a 4, 14, 34 and 49% improvement in PASI 75 in placebo in the low-, medium- and high-dose etanercept groups, respectively and it was statistically significant in all three groups compared with placebo. At the end of 24 weeks 25, 44 and 59% of the patients showed an improvement of 75% or more in the PASI in the low, medium and high dose etanercept groups. 33% of the patients who were crossed over to receive etanercept after 12 weeks of placebo showed 75% improvement in the PASI. There was a statistically significant improvement in patient’s global assessments of the disease and in the as assessed by the DLQI. Efficacy was dose-related and with continuous treatment there is a sustained benefit for 24 weeks.

A total of 112 patients were randomized for placebo (n = 55) or etanercept (n = 57) 25 mg subcutaneously twice a week for 24 weeks in a double-blind, placebo-controlled, multicenter study [54]. At week 12, PASI 75 was achieved in 30 and 2% of patients and at week 24, PASI 75 was achieved in 56 and 5% of patients in the etanercept- and placebo-treated subjects, respectively. There was consistent improvement in the physician global score, patient global score, and DLQI.

A global, randomized, Phase III, placebo-controlled trial enrolled patients to receive etanercept twice-weekly at a dose of 50 or 25 mg subcutaneously or placebo twice-weekly in a double-blind fashion during the first 12 weeks of the study [55]. All patients received 25 mg twice-weekly during the second 12 weeks. Out of the 583 randomized subjects, 49, 34 and 3% of subjects in the etanercept 50- and 25-mg twice-weekly group, and placebo respectively, achieved PASI 75 at week 12 (p < 0.0001 for each etanercept group compared with placebo). At week 24 (after 12 weeks of open-label 25 mg etanercept...
twice-weekly), 54% of patients whose dose was reduced from 50 to 25 mg twice-weekly, 45% of patients in the continuous 25 mg twice-weekly group and 28% of patients in the group that received placebo followed by etanercept 25 mg twice weekly achieved PASI 75. Etanercept was well tolerated throughout the study.

**Long-term treatment**

Although treatment response in severe, recalcitrant disease, erythrodermic, pustular or other forms of psoriasis is unknown, studies have shown consistent benefit over time without loss of efficacy over a 1-year period [37].

**Infliximab**

A total of 11 patients were enrolled in each arm of a randomized, controlled clinical trial carried out by Chaudhari and colleagues evaluating placebo and 5 and 10 mg/kg infliximab at 0, 2 and 6 weeks [56]. Clinical improvement in terms of physician’s global assessment score (good, excellent or clear rating) were observed in 82 and 91% of patients treated with infliximab 5 and 10 mg/kg respectively, versus 18% in the placebo-treated group. The study was extended in an open-label phase from weeks 10–26 [57]. The nonresponding patients, as well as patients with relapse of the disease (i.e., with loss of 50% benefit in PASI in the placebo group) were randomized for 5 or 10 mg/kg of infliximab at weeks 0, 2 and 6, and then followed up for the total period of 26 weeks. The patients who received 5 or 10 mg/kg infliximab in the first part of the study and relapsed during the 26-weeks period received a single dose of infliximab of the same strength. The patients who received 10 mg/kg in the first part of the study and relapsed were dropped from the study while nonresponders in the 5mg/kg group received a single dose of 10 mg/kg and followed up for 26 weeks. Among all patients treated with infliximab (17 out of 30), PASI 50 and PASI 75 were maintained in 57 and 50% of patients at week 26, while PASI 50 and PASI 75 were maintained in 40 and 33% of the patients who received 5 mg/kg and in 73 and 67% of patients who received 10 mg/kg at the end of 26 weeks.

This multicenter, double-blind, placebo-controlled, randomized trial involved 249 patients with severe plaque-type psoriasis [58]. Patients received either placebo or 3 or 5 mg/kg infliximab at weeks 0, 2 and 6, followed by intravenous infusion of their assigned study treatment at week 26 if they showed moderate-to-severe disease activity on physician global assessment score. Response was seen as early as 2 weeks in 34–40% patients. At week 10, 72 and 88% of patients treated with 3 and 5 mg/kg infliximab respectively, achieved 75% or greater improvement in PASI compared with 6% in the placebo group. There was also a substantial improvement in DLQI, making this the most effective biological treatment for psoriasis and the only agent more effective than cyclosporin and MTX. The maximum response in PASI started to decline at 10 and 14 weeks in the 3 and 5 mg/kg infliximab-treated groups, respectively.

Infliximab has been shown to be effective in both an induction and maintenance treatment of moderate-to-severe psoriasis in this recent Phase III, multicenter, double-blind trial [59]. A total of 378 patients were allocated infliximab 5 mg/kg or placebo infusions at a 4:1 ratio at weeks 0, 2 and 6, and then every 8 weeks to week 46. Placebo-treated patients crossed over to infliximab treatment at week 24.

Of the patients treated with infliximab, 80 and 57% achieved PASI 75 and PASI 90, respectively, compared with 3 and 1% in the placebo group at 10 weeks. PASI 75 and PASI 90 were maintained in 82 and 58% of patients at week 24. In addition, PASI 75 and PASI 90 were achieved in 61 and 45% of patients at week 50.

**Concomitant therapy with other systemic agents**

Although the therapeutic and safety benefits of combination therapy in psoriasis remain to be established, the use of this treatment method in combination with cyclosporin, acitretin, MTX and hydroxyurea has been reported in a case series [60,61]. Concomitant therapy can be used in combination with other systemic treatments when attempting to introduce infliximab in a patient already receiving other systemic agents, where it is not possible to introduce a sudden withdrawal of a drug and where infliximab as a monotherapy is ineffective [37].

**Adalimumab**

**Efficacy & long-term treatment**

The short- and long-term efficacy of adalimumab has been evaluated in this randomized, double-blind, placebo-controlled trial for the initial 12 weeks, followed by open-label extension for a further 48 weeks [62]. Initially, 148 patients were randomized to receive...
- 80 mg adalimumab at week 0, then 40 mg adalimumab every other week beginning at week 1
- 80 mg adalimumab at weeks 0 and 1, then 40 mg weekly beginning at week 2
- Placebo weekly beginning at week 0

Out of 137 patients who completed the study at week 12, PASI 75 or more was achieved by 53% on 40 mg every other week, 80% on 40-mg weekly and 4% patients on placebo. After week 12 in the extension trial, patients who were receiving adalimumab continued on the same doses and patients who were receiving placebo were given 80 mg at week 1 followed by 40 mg adalimumab every other week. At week 24, 67% of patients on alternate-week adalimumab and 77% of patients on weekly adalimumab achieved a greater than or equivalent to PASI 75. At week 60, the greater than or equivalent to PASI 75 response was maintained in 67 and 73% of patients receiving adalimumab every other week and every week, respectively, and a PASI 90 response was achieved in 36 and 55% of patients, respectively. Statistically significant improvement in questionnaires, including short form (SF)-36, EuroQol (EQ)-5D and DLQI, were also noted at 48 weeks of therapy with adalimumab [63,64,65].

Another randomized, double-blind, placebo-controlled trial to evaluate the efficacy of adalimumab in psoriatic arthritis enrolled 151 patients in an adalimumab group and 164 patients in a control group. A total of 69 patients in each group had skin psoriasis involving at least 3% of the body surface area and they were evaluated for PASI response. At week 24, 59% of adalimumab-treated patients achieved PASI 75 as compared with 1% of placebo-treated patients. In addition the significant improvement in PASI response was noted as early as 4 weeks and the improvement was similar in mild, moderate (PASI ≤ 10 at baseline) and severe (PASI > 10 at baseline) psoriasis [66].

**Anti-TNF agents**

Adalimumab has been used with MTX for the treatment of rheumatoid arthritis without increase in the incidence of the adverse events except for injection site reactions. [67].

**Side effects**

Although these three TNF-α inhibitors have only recently being used for the treatment of psoriasis, they have been in use for more than 5 years in rheumatoid arthritis and psoriatic arthritis, often in combination with MTX or at different doses than those used in psoriasis, and the following side effects have been reported.

**Injection-site reactions**

Mild-to-moderate injection-site reactions comprising erythema, edema and bruising have been the most frequently reported adverse event with etanercept and adalimumab [39,68].

**Hypersensitivity reactions**

Mild hypersensitivity reactions are common with infliximab, and may rarely include anaphylactic reactions, convulsions, erythematous rash and hypotension [37]. Approximately 1% of patients receiving adalimumab developed allergic rash, fixed-drug eruption, urticaria and anaphylactoid rash (anaphylactic reaction is rare) [39]. Allergic reactions reactions to etanercept are common and included urticaria and angioedema [68].

**Serious infections**

Overall, infection rates requiring intravenous antibiotics or hospitalization are similar to the placebo group for all three anti-TNF agents [39,68,69]. Infections involving all organ systems and a few cases of tuberculosis (TB) have been reported with the use of etanercept and adalimumab in patients with rheumatological disorders [39,68]. TB and sepsis secondary to *Listeria monocytogenes* [71] and histoplasmosis [72] have been identified in subjects treated with infliximab for diseases other than psoriasis [73], the majority of which were also receiving one or more other immunosuppressive agents. It is estimated that the risk of TB is six-times higher in patients treated with infliximab [74]. Infections caused by viruses, bacteria, fungi and protozoa and involving all organ systems have been reported with adalimumab, including few fatal TB and opportunistic infections [39].

**Neurologic diseases**

Although the causal relationship remains unclear, cases of transverse myelitis, optic neuritis, multiple sclerosis and new-onset seizure disorders have been described with etanercept and infliximab treatment [74,75]. Use of adalimumab has rarely been associated with new cases of multiple sclerosis, Guillaine-Barre syndrome and nonspecific demyelination [39,76].

**Malignancy**

Etanercept has been associated with a threefold higher rate of development of lymphoma when
Biological treatments for psoriasis – REVIEW

used for rheumatological disease [68] and Infliximab is associated with about six fold higher rate of lymphoma in combined population of crohn’s disease and rheumatological diseases [75]. However this may be a feature of the severity of the disease and other concomitant therapy or prior immunosuppressants used in these patients who have an increased risk of similar magnitude without anti-TNF-α therapy. More cases of malignancy have been observed in adalimumab-treated patients, including lymphomas, compared with controls, although the standardized incidence ratio (SIR) for the development of lymphoma is similar to other rheumatoid arthritis patients naive to TNF-α agents [39,76].

Cardiovascular disease
Etanercept, infliximab and adalimumab have been associated with worsening of congestive heart failure and, to a lesser extent, with new-onset congestive heart failure in patients without pre-existing heart disease [39,76,77].

Hematologic events
Although a causal relationship is unclear, rare cases of aplastic anemia have been reported with the use of etanercept and adalimumab and medically significant cytopenias including neutropenia, thrombocytopenia, leukopenia and pancytopenia have been reported with the use of all three anti-TNF-α agents [38,39,68].

Hepatotoxicity & hepatitis
Infliximab therapy has been associated with rare cases of severe hepatitis reaction [37]. Concomitant use of antiviral therapy has been recommended in patients with hepatitis B and C with immunosuppressive agents including TNF blockers [78].

Antinuclear antibodies & lupus-like syndromes
Development of lupus-like syndromes that resolved spontaneously on drug withdrawal has been reported with etanercept and with infliximab [79,80] when used for diseases other than psoriasis. Systemic lupus erythematosus (SLE) and lupus-like syndromes have rarely been associated with adalimumab but the overall incidence does not appear to increase with adalimumab [74].

The importance of antibody development against biologic agents
Etanercept has been associated with the development of antibodies against the drug in approximately 6% of treated patients; however, the clinical relevance of this observation has not yet been established [68]. The incidence of the development of antibodies against infliximab has been reported between 8–61% in patients with rheumatoid arthritis and Crohn’s disease and psoriasis [81]. Antibodies were found more frequently in patients with Crohn’s disease and patients who were not receiving other immunosuppressive agents, such as MTX or azathioprine. The clinical significance of antibody development in psoriasis is not clear, but in other diseases it has been associated with a higher risk of infusion reactions and shorter duration of response [37,81]. Antibodies to adalimumab developed in 12% of patients who were treated with humira and 7% of placebo and active control-treated patients

<table>
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<th>Highlights</th>
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<td>The immunopathogenesis of psoriasis can be summarized in three steps:</td>
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<td>• T-cell activation: T cells are activated on exposure to an unknown antigen Langerhans’ by expressing the antigen and migrating to regional lymphnodes.</td>
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<td>• Trafficking of activated T cells into the skin: the activated T cells migrate to the skin by interaction between different adhesion molecules.</td>
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<td>• Positive feedback cycle of continuous T-cell activation in the skin: The cytokines produced by T cells, macrophages, antigen-presenting cells and keratinocytes cause psoriasis skin changes as well as continuous T-cell activation.</td>
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<td>• Recently, selectively immunologically directed treatments, known as biologics, have been developed. Biologic treatments include recombinant cytokines, monoclonal antibodies and fusion proteins directed against specific events in the pathogenesis of psoriasis and include:</td>
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<td>• Alefacept: once-weekly intramuscular dose, CD4+ lymphocyte-count monitoring required.</td>
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<td>• Efalizumab: once-weekly subcutaneous injection. Platelet-count monitoring required.</td>
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<tr>
<td>• Etanercept, infliximab and adalimumab (antitumor necrosis factor TNF-α agents): probably more effective.</td>
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at week 24 in arthritis trials [39]. However, again, the significance of this phenomenon is unknown. The incidence of antibodies in two biologics, alefacept and efalizumab, which have been approved only for psoriasis, is 3 and 6.3% respectively. This has not been associated with a significant change in adverse events or worse clinical outcome [81].

Pretreatment evaluation & monitoring

**Evaluation**

All patients should have the following:

- Comprehensive review including detailed history, physical examination and necessary investigations based on side effects, cautions and contraindications of individual biologic agents. Particular emphasis should be placed on detection of infection and malignancy, including skin malignancy, demyelination and heart failure for anti-TNF-α agents;
- Patients about to start TNF-α inhibitors should be screened for TB with chest x-ray and/or tuberculin test;
- PASI, DLQI and where appropriate, assessment of joints in accordance with the British Society of Rheumatology guidelines;
- Full blood count, liver function tests, urea and electrolytes, autoantibodies, hepatitis B and C screening, urine analysis, chest x-ray and HIV test if required.

**Monitoring**

Monitoring should be carried out at 3 months and then 6-monthly. All patients should have the same criteria as for the evaluation, apart from hepatitis screening, autoantibodies, TB screening and chest x-ray [37]. In addition, patients on alefacept require CD4+ counts every 2 weeks [80] and patients on efalizumab require monthly full blood counts for the initial 3 months followed by every 3 months due to the risk of thrombocytopenia [33].

**Choice of biological agent**

There are currently no studies directly comparing these biological agents for psoriasis. From the existing, published clinical studies, infliximab and adalimumab (once a week) appears to be more effective in the short term at 12 weeks. There is no evidence to indicate the superiority of one agent over the other in terms of efficacy and safety [37].

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Biological treatments for psoriasis – REVIEW

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436

Therapy (2006) 3(3)