REVIEW ARTICLE

Drug Safety 2006; 29 (1): 49-66
0114-5916/06/0001-0049/$39.95/0

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Fulfilling an Unmet Need in Psoriasis

Do Biologicals Hold the Key to Improved Tolerability?

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Contents

Abstract

Psoriasis is a chronic inflammatory disease of the skin affecting approximately 2% of the world's population. Traditional systemic treatments, including methotrexate, ciclosporin, psoralen plus UVA (PUVA), oral retinoids and fumaric acid esters, are widely used for severe disease and are effective in the short term. Severe psoriasis is a chronic disease and patients and physicians have expressed concerns about possible harm from organ toxicity, such as skin cancer (PUVA), hyperlipidaemia (retinoids), renal (ciclosporin) or hepatotoxicity (methotrexate). Long-term monitoring is required and may not detect early organ damage. The pathophysiology of psoriasis remains to be clarified, but advances toward the understanding of the immunological basis of psoriasis have uncovered the involvement of immunological pathways; for example, the role of tumour necrosis factor (TNF)-α, T cell proliferation and T cell activation, and migration to the epidermis. This advancement in knowledge combined with developments in recombinant technologies has led to the development of target-specific therapies.

Biological agents are defined as proteins that can be extracted from animal tissue or produced via recombinant DNA technologies and possess pharmacological activity. Adalimumab, alefacept, infliximab, efalizumab and etanercept are examples of biological agents currently used for the treatment of psoriasis. Some of these are also therapy for other autoimmune conditions, such as rheumatoid arthritis and Crohn's disease. These biological agents are effective in psoriasis but raise new safety concerns. Information on the safety of biological agents in conditions such as rheumatoid arthritis and Crohn's disease can not be directly extrapolated to psoriasis. An increased incidence of lymphomas has been postulated to be associated with etanercept, infliximab and adalimumab; serious infections, such as tuberculosis, have also been reported with these three biologicals, all of which target TNF-α. Demyelinating disorders, such as multiple sclerosis, have been reported with some biologicals as has congestive heart failure. Alefacept, because of its mechanism of action of lowering the number of active T cells, is associated with low T cell counts. Efalizumab has been associated with thrombocytopenia and haemolytic anaemia. Data on the safety of >2.5 years' continuous treatment with efalizumab are reassuring and a valuable beginning to understanding the role and risk of harm of long-term therapy for a chronic disease. Longer follow-up studies and safety databases, for each of the biologicals used in psoriasis, are needed to ensure both prolonged efficacy and minimal risk of harm.

Psoriasis is a chronic inflammatory disease of the skin affecting approximately 2% of the world's population.[1] It is characterised by the appearance of thick and scaly erythematous plaques commonly found on the scalp, elbows, legs and knees.[1] Psoriasis causes itching and burning pain, and has a significant impact on a patient's quality of life. Indeed, the detrimental effects of the disease on the physical and mental state of patients with psoriasis are well documented.[2-4] However, disease severity can differ among individuals. Approximately 70% of people affected with the disease have mild-to-moderate psoriasis,[5] but 30% have moderate-to-severe psoriasis, which is defined as having >3% of the body surface area affected.[6]

Given the distinctive thickening of the epidermis, keratinocyte proliferation was the focus of early research into psoriasis. However, since the serendipitous observation that ciclosporin, a drug known to inhibit T cell activation and cytokine release, resolved concurrent psoriasis in a patient with rheumatoid arthritis,[7] the basis of psoriatic treatment has been revised. It is now realised that T cell infiltration and activation play a primary role in the pathogenesis of psoriasis, with the resulting keratinocyte hyperplasia being a secondary response.[8-10]

Local, topical treatments such as vitamin D analogues, corticosteroids, tars, dithranol and retinoids have proven efficacy in the treatment of mild-to-moderate psoriasis.[11] However, treatment of more severe cases of psoriasis, involving large areas of the body, requires a systemic approach.

Traditional systemic treatments for moderate-to-severe psoriasis include ciclosporin, oral retinoids, methotrexate, UV phototherapy and fumaric acid. These treatments have been widely used and are effective in the short term, yet all have drawbacks that limit their utility (for a summary of such safety concerns, see table I).

As knowledge about the pathogenesis of psoriasis continues to build, new classes of agents for the treatment of moderate-to-severe psoriasis are being developed. These new systemic agents, created using advanced biotechnology, target specific immunological processes that consequently reduce the multiple organ toxicity and adverse effects that are associated with traditional treatments.

The aim of this review is to discuss the safety and efficacy profiles of these new systemic agents in comparison with the traditional, nonbiological treatments for moderate-to-severe psoriasis (for a summary of the safety concerns associated with the

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biological therapies, see table II). Literature searches were performed using MEDLINE and general internet sources (e.g. Google) from March 2004 to April 2005. Search terms included: 'systemic', 'biologic/biological', 'treatments/therapies', 'moderate-to-severe psoriasis' and 'safety/tolerability'. Newer important data were added on an *ad hoc* basis if they were published, or posted on a regulatory website, after April 2005.

Table I. Summary of safety concerns associated with traditional, nonbiological treatments for moderate-to-severe psoriasis

Drug	Safety concern
Methotrexate	Fetal death and/or abnormalities Myelosuppression (leukopenia, anaemia, macrocytic anaemia, thrombocytopenia) Hepatotoxicity Pulmonary fibrosis Severe skin reactions Severe opportunistic infection Lymphoproliferative disorders Gastrointestinal disorders Constitutional symptoms Acute effects (hypersensitivity, nausea, fatigue)
Ciclosporin	Nephrotoxicity Hypertension Immunosuppression (increased risk of infection and malignancy) Hypomagnesmia Elevated triglyceride and cholesterol levels Cutaneous malignancies
Psoralen plus UVA	Photodamage and premature skin aging Increased risk of melanoma and non-melanoma skin cancers (dose related) Ocular damage Acute effects: pruritus, nausea and delayed sunburn-like erythema
Oral retinoids (acitretin)	Fetal death and/or abnormalities Hepatotoxicity Hypertriglyceridaemia, hypercholesterolaemia, and reduction in HDL-C levels Dose-related alopecia Mucocutaneous toxicity *Less commonly*: ophthalmological symptoms (e.g. dryness) and arthralgia, myalgia, paresthesia or worsening of pre-existing bone disorders during long-term therapy
Fumaric acid esters	Gastrointestinal symptoms Flushing Transient renal damage

HDL-C = high-density lipoprotein cholesterol.

1. Traditional Nonbiological Treatments for Moderate-To-Severe Psoriasis

1.1 Methotrexate

Methotrexate is a well established systemic agent used for the treatment of psoriasis and its efficacy is widely accepted.[1,5] The first reports on the use of methotrexate were published in the 1960s.[12] This folic acid antagonist competitively inhibits the enzyme dihydrofolate reductase, preventing the conversion of dihydrofolate to tetrahydrofolate, an essential cofactor in the synthesis of the pyrimidine and purine nucleotides required for DNA and RNA synthesis.

Methotrexate is seen by many as the gold standard of treatment for severe psoriasis,[11] although no placebo-controlled trials have been performed. Only one randomised, controlled trial comparing methotrexate (n = 44) and ciclosporin (n = 44) in terms of efficacy, tolerability and effects on quality of life (QoL) has been reported.[13] Efficacy, measured in terms of remission, was similar between the two agents: 60% of methotrexate-treated patients and 71% of ciclosporin-treated patients achieved partial remission, defined as a reduction from baseline in the psoriasis area and severity index (PASI) score of ≥75%. QoL assessments were also similar between the two treatment groups; however, almost one-third of the patients (27%) receiving methotrexate withdrew from the study because of adverse effects, compared with just one patient (2.3%) treated with ciclosporin.

Despite being an established treatment for severe psoriasis, the use of methotrexate is contraindicated in certain patient groups. The following is a list of the full exclusion criteria:[1]

- pregnancy
- renal impairment
- recent hepatitis
- pre-existing cirrhosis or pronounced liver fibrosis
- excessive alcohol intake
- patient unreliability

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- unwillingness to adopt monitoring measures
- unwillingness to use contraception
- active peptic ulcers
- severe infection
- pronounced anaemia
- leukopenia
- thrombocytopenia.

Since 85% of the drug is excreted via the kidneys, accumulation of methotrexate, caused by low clearance rates in patients with renal disease, can lead to leukopenia and acute gastrointestinal complaints.[14] Indeed, most of the associated adverse effects occur as a result of the accumulation of methotrexate and end-organ toxicity, therefore, intermittent therapy is advised.

Cirrhosis of the liver in methotrexate-treated patients has also been widely reported and has forced new guidelines to be published with regard to treatment regimens and monitoring (see table III).[15] The risks to the liver are managed by lifestyle changes, such as avoiding alcohol intake and taking folic acid supplements. Regular liver function tests are now a standard monitoring procedure for all methotrexate-treated patients although newer tests, such as the assessment of procollagen III levels, are not widely available. Liver biopsies are required in patients with a history of liver disease and in those receiving high doses of methotrexate; however, there is conflicting advice from different authorities regarding the timing of such biopsies. A common suggestion is to perform a biopsy for every 1.5–2.0g of methotrexate ingested. Hepatotoxicity resulting from methotrexate treatment precludes its use in patients with pre-existing cirrhosis and in those unable to restrict their alcohol intake.

Table II. Summary of safety concerns associated with biological therapies for moderate-to-severe psoriasis

Drug	Safety concern
Infliximab[a]	Infusion-related reactions Infection, including tuberculosis Malignancy/lymphoproliferative disease[b] Worsening heart failure[c] Antichimeric antibodies
Etanercept	Serious infection (tuberculosis) Worsening heart failure[c] Neurological events[d] Pancytopenia[d] Malignancy[d] Injection-site reactions
Adalimumab	Infections (tuberculosis, respiratory tract infections) Injection-site reactions Lymphoma[e] Hypersensitivity reactions Neurological events[e]
Alefacept	Lymphopenia Malignancy
Efalizumab	Psoriasis (immune-mediated)[f]

a Not yet approved for the treatment of psoriasis.

b Insufficient data to determine whether infliximab contributed to the development of the malignancies.

c In patients with moderate-to-severe heart failure.

d Rare (cause unclear).

e Insufficient data to determine whether adalimumab has a direct casual relationship with this adverse effect.

f Worsening and/or variant.

1.2 Ciclosporin

Ciclosporin blocks the intracellular components of T cell activation, which in turn inhibits the production of cytokines, including interleukin (IL)-2 (a cytokine known to exacerbate psoriasis).[1] Taken orally, ciclosporin therapy is indicated in patients who have psoriasis that has not responded to at least one other form of systemic therapy (including phototherapy, methotrexate and oral retinoids) or for whom other systemic therapies are contraindicated or poorly tolerated. Patients find this treatment easy to take and it has a relatively rapid onset of action.[1]

A meta-analysis, which included 579 patients from three studies, revealed that twice-daily ciclosporin treatment (5mg/kg/day) mediated a reduction in PASI score of 72%.[16] Furthermore, ciclosporin was significantly superior to etretinate, an oral retinoid, for the treatment of psoriasis. The study concluded that, despite its efficacy, ciclosporin should only be used for short-term treatment because of concerns about its safety.

Impaired renal function, hypertension, hypomagnesaemia, elevated serum creatinine, cholesterol and triglyceride levels, as well as cutaneous malignancies, are all known adverse effects following long-term treatment with ciclosporin.[5,17,18]. Although careful patient selection and regular follow-up visits and monitoring may limit these unwanted effects (see table III),[11,19] in practice patients may find the constant visits and checks burdensome.

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Table III. Monitoring required by patients receiving the more traditional treatments for moderate-to-severe psoriasis

Timing of monitoring	Methotrexate	Ciclosporin	PUVA	Acitretin
Baseline	Laboratory evaluation (including CBC with differential and platelets, hepatic enzymes and renal function) Chest x-ray Pregnancy	Dermatological and physical exam (including blood pressure) Laboratory evaluation (including serum creatinine, electrolytes, LFT, BUN, CBC, serum magnesium, potassium, uric acid and lipids) Presence of occult infection or malignancy	Ophthalmological exam Routine laboratory evaluation	Pregnancy
During treatment	Adverse events Regular laboratory evaluation including CBC with differential and platelets at least monthly, liver and renal function tests at least every 2 months, chest x-ray Liver biopsy at a cumulative dose of 1.5g (in patients with no known risk factors) or PIIINP assessment (not fully validated in clinical practice) Infection or malignancy	Adverse events Laboratory evaluation at least every 2 weeks until findings stabilise, then monthly, including blood pressure Infection or malignancy	Adverse events Skin cancers Ophthalmological exam Routine laboratory evaluation	Adverse events Regular laboratory evaluation, including blood sugar, lipids and LFT
Patient characteristics indicating the need for special care	Impaired renal function, ascites or pleural effusions Elderly patients	History of PUVA and to a lesser extent, methotrexate or other immunosuppressive agents, UVB, coal tar or radiation therapy Elderly patients	Erythrodermic psoriasis Multiple basal cell carcinomas or a history of basal cell carcinoma History of x-ray or grenz ray therapy, prolonged tar and UVB therapy or arsenic exposure Hepatic insufficiency Concomitant therapy with known photosensitising agents Elderly patients	High risk of developing hyperlipidaemia

BUN = blood urea nitrogen; **CBC** = complete blood cell count; **LFT** = liver function tests; **PIIINP** = amino terminal propeptide of type III procollagen; **PUVA** = psoralen plus UVA radiation.

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1.3 Oral Retinoids

The retinoids comprise vitamin A and its natural and synthetic analogues. Their immunomodulating and cell-differentiating abilities in a number of cell types, including keratinocytes, lymphocytes, neutrophils and fibroblasts, mean that retinoids are indicated in a number of dermatological diseases, including psoriasis.[1] The retinoids mediate their action via nuclear receptors that influence gene transcription and subsequent protein synthesis.

Two vitamin A analogues are available, etretinate and its metabolite acitretin (although only the latter is approved for the treatment of psoriasis in the US and most European countries).

Mucocutaneous toxicities are the most common adverse effects reported with the use of oral retinoids, and these are generally dose dependent and reversible.[20] Elevated liver enzyme and serum triglyceride levels have also been observed during retinoid treatment,[1] which in turn require regular monitoring (table III). In addition, retinoids are known teratogens, thus preventing their use in women who are pregnant, breastfeeding or those who may become pregnant within 2 years.[1]

1.4 UV Phototherapy and Photochemotherapy

Photoimmunological agents use nonionising electromagnetic radiation, including UV, to modulate the immune system.[21] Although UVB radiation is an effective immunomodulator, its effects are limited to the epidermis. Psoralen, a photosensitising chemical, plus UVA radiation (PUVA) has a valuable place in the antipsoriatic armamentarium. Photoimmunological agents exert their effects via soluble mediators (e.g. they induce anti-inflammatory agents), modulation of cell-surface receptors and UV-induced apoptosis.[21]

Although PUVA and phototherapy have proven efficacy, their long-term use is, inevitably, associated with an increased incidence of skin cancer.[5,22,23] Indeed, there is uncertainty among physicians regarding the benefit-risk ratio.[24,25] Precautionary guidelines are in place that limit the accumulative exposure to <200 treatments per patient. It has also been suggested that contraindications should be extended to include a personal or family history of melanoma.[24] Gastrointestinal upset (which is often the cause for discontinuation of this line of therapy) and cataracts are also common. An additional disadvantage of PUVA treatment is that the course and nature of the therapy itself requires frequent patient travel to a clinic for treatment; undoubtedly, this would have quite an impact on the patient's lifestyle and compliance with such a regimen may suffer. Also, the psoralen used in PUVA therapy is metabolised in the liver and, consequently, regular liver function tests (LFTs) are required in order to monitor possible liver damage (see table III for the monitoring required during PUVA therapy). However, cessation of PUVA because of abnormal LFTs is rare.[17]

1.5 Fumaric Acid Esters

Although not extensively used, fumaric acid esters (fumarates) are indicated for severe psoriasis in certain parts of Europe. These compounds promote the secretion of IL-4, IL-5 and IL-10 and inhibit interferon-γ, which is a modification in the cytokine profile that is associated with improvements in the symptoms of psoriasis.[5] Although there are no studies comparing this with other systemic therapies,[5] a recent study reported that >80% of patients achieved complete clinical remission following 6 months' treatment with dimethylfumarate.[26]

Safety concerns about long-term fumaric acid use have been expressed since the 1980s.[5] Approximately two-thirds of patients treated with fumaric acid experience gastrointestinal symptoms and one-third develops flushing, although this appears to diminish with ongoing treatment.[5] Long-term administration of fumaric acid has been associated with a transient increase in liver enzyme levels[27] and with kidney damage.[28]

The efficacy of oral fumaric acid in psoriasis may be improved (and therefore adverse effects may be limited) if it is used in combination with a topical treatment.[5,29]

2. Into the Age of 'Biological' Antipsoriatic Therapies

Advances in the knowledge of the pathogenesis of psoriasis have allowed the development of target-specific therapies. A better understanding, coupled

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with developments in recombinant technologies, has led to the production of proteins that can modulate immune responses, which in turn has led to more effective therapies, with the potential to improve tolerability and safety.

'Biological' agents, defined as proteins that possess pharmacological activity that can be extracted from animal tissue or produced via recombinant DNA technologies,[9] are still being developed and refined. As the revolution in psoriatic treatment continues, lessons are being continually learned and improved treatments are becoming available. A number of important, new therapeutic agents have been developed to modulate specific immune responses.

2.1 Immunological Proteins

Antibodies are proteins that are involved in the immune system and are alternatively known as immunoglobulins. Each antibody consists of four polypeptides: two heavy chains and two light chains joined to form a Y-shaped molecule. The amino-acid sequence on the tips of the 'Y' varies greatly between antibodies. This so-called variable region, composed of 110–130 amino acids, engenders antigen-binding specificity, and cleavage of this region by proteases produces the antigen-binding fragment (Fab). The constant region not only determines the mechanism used to destroy the antigen but also the classification of the antibody.

Monoclonal antibodies are produced by fusing single antibody-forming cells to tumour cells grown in culture. The result is called a hybridoma and each produces relatively large quantities of identical antibody molecules when cultured. Monoclonal antibodies are produced by clones of a single antibody-producing cell.

In the early 1980s, recombinant DNA technology was applied to antibody design to reduce the antigenicity of murine and other rodent-derived monoclonal antibodies. Chimeric antibodies have murine variable regions combined with the constant domains of the human IgG molecule. The chimeric antibody is less likely to provoke an immune response than a murine monoclonal antibody, but it does not eliminate the risk of such a response. Further developments have produced partly humanised antibodies, deimmunised antibodies and primatised antibodies. Human antibodies developed from murine sources and transgenic techniques have also been developed.

Dimeric antibodies are composed of two IgG molecules linked together via a disulphide bond, forming a homodimeric antibody.

2.2 The Immunological Basis of Psoriasis

T cell activation is a fundamental event in the aetiology of psoriasis. This occurs when antigen-presenting cells (APCs) expose antigens to memory T cell receptors. However, in order for the T cell to recognise the antigen, signals are required and these take the form of protein-protein interactions between the APC and T cell.[10] These signals result in the two cells binding together and the subsequent activation of the T cell, which is then referred to as an effector T cell. A number of biological agents have been developed to interfere with this activation and signalling process, thus inhibiting T cell activation.[9,30]

In the lymph node, activated T cells undergo proliferation and create T cell clones that increase in number according to the immune response. Cytokines produced by the T cells play a part in the signalling and proliferation process.[30] During the maturation process, T cells acquire new adhesion molecules that direct the T cells to sites of cutaneous inflammation; this process is also known as trafficking. Effector T cells in the dermis or epidermis release cytokines that attract and direct fellow T cells and other inflammatory mediators, which results in the psoriasis phenotype. Figure 1 summarises these events schematically.[31,32]

This cascade of events provides several windows of opportunity for intervention with biological agents. The main therapeutic targets, also outlined in figure 2,[32,33] are:

- inflammatory mediators, including cytokine messengers (e.g. tumour necrosis factor [TNF]-α) from effector T cells;
- T cell proliferation;
- T cell activation and migration to the epidermis.

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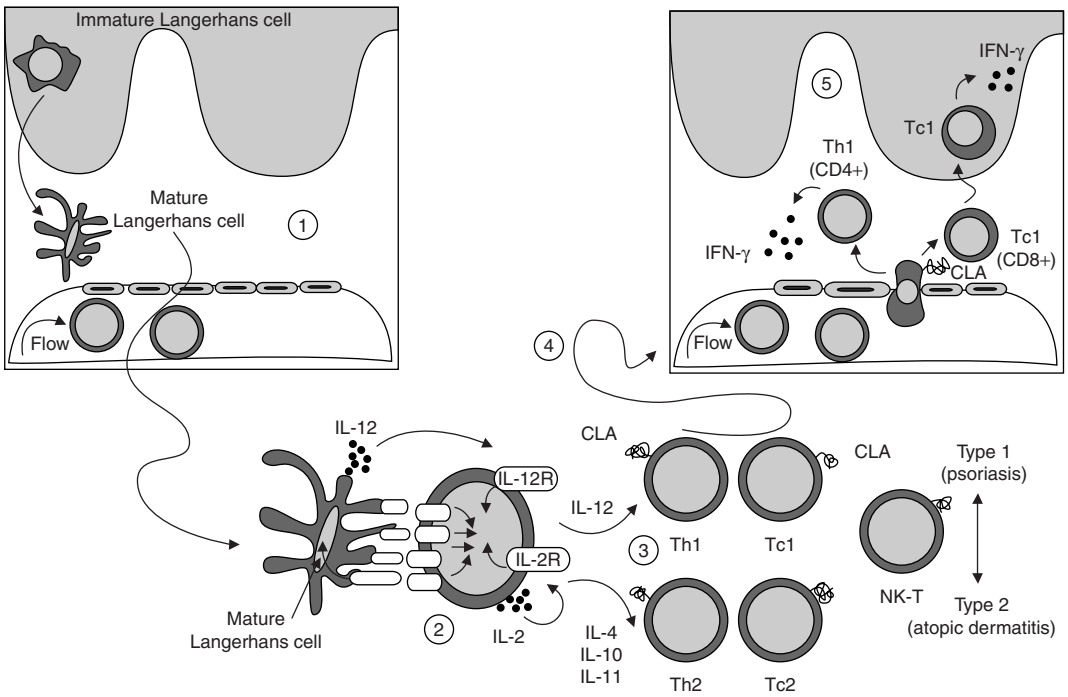

Fig. 1. Generation of a cutaneous T cell immune response *de novo*. Cellular immune activation and trafficking pathways of Langerhans cells and T cells during an immune response. (1) Antigen capture by immature Langerhans cells in the epidermis activates maturation and migration of cells to skin-draining lymph nodes. (2) Molecular interactions between a mature Langerhans cell (antigen-presenting cell) and a naive T cell in a lymph node activates the T cell. (3) Activated lymphocytes acquire the skin-homing receptor, cutaneous lymphocyte antigen (CLA) and differentiate into type 1 or type 2 effector lymphocytes. (4) CLA positive (CLA+) memory T cells enter the circulation and exit cutaneous blood vessels at sites of inflammation. (5) T cells in the dermis or epidermis become activated to release cytokines (or exert other effector actions) on encountering the initiating antigen. Psoriasis is a disease in which type 1 T cells are expanded and effector actions in skin involve the release of interferon (IFN)-γ as shown. In normal immune responses, antigens are eliminated by T cell stimulated pathways in the skin and then the immune response ceases. In psoriasis, T cell infiltration and effector responses persist chronically (reproduced from Krueger,[31] with permission). **IL** = interleukin; **IL-2R** = interleukin-2 receptor; **IL-12R** = interleukin-12 receptor; **NK-T** = natural killer T cells; **Tc1** = type 1 cytotoxic T cells; **Th1** = type 1 helper T cells.

3. Currently Available Biological Agents

3.1 Tumor Necrosis Factor-α Inhibitors

3.1.1 Infliximab

Infliximab, a chimeric (mouse-human) monoclonal antibody against TNF-α, was originally designed for use in the treatment of rheumatoid arthritis and Crohn's disease, indications for which it is currently approved in the US and Europe. More recently, infliximab has been approved for use in the treatment of psoriatic arthritis in Europe, but is not yet approved for the treatment of psoriasis. This agent also inhibits the production of other proinflammatory cytokines that decrease cell infiltration and, ultimately, keratinocyte proliferation.[34] In the treatment of Crohn's disease and rheumatoid arthritis, infliximab is administered as an intravenous (IV) infusion (3–10 mg/kg), which is repeated after 2 and 6 weeks.[35] A similar regimen was used in a randomised, controlled trial investigating the efficacy and safety of infliximab in psoriasis.[36] The study demonstrated that patients receiving infliximab experienced a more rapid response than those receiving placebo; differences between the placebo and the active treatment groups were apparent as early as week 2 of treatment.[36] Furthermore, 73–82% of patients receiving infliximab had an improvement in

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PASI score of at least 75%, compared with 18% of placebo-treated patients.

Information regarding the safety of infliximab is extensive because of its widespread use in patients with rheumatoid arthritis and Crohn's disease. Indeed, approximately 280 000 patients have been treated with infliximab.[35] Since the regimens for the treatment of these diseases and psoriasis are similar, it is plausible to extend the safety profile gained for the treatment of rheumatoid arthritis and Crohn's disease to that expected during psoriasis treatment.

Infusing or injecting foreign particles into the body can initiate an antibody response, which can increase the potential for subsequent reactions during infusion. Indeed, patients should also be monitored for delayed hypersensitivity reactions and the appearance of lupus-like illness. Such a response renders the treatment ineffective and precipitates a symptomimetic immune response. Treatment should be discontinued if these symptoms occur.

Another concern reported for infliximab is the formation of human antichimeric antibodies; 13% of patients with Crohn's disease, rheumatoid arthritis and other indications who were treated with infliximab and were followed up for 3 years, developed antibodies.[37] Formation of such neutralising antibodies may affect the efficacy of infliximab and patients may require higher doses to maintain control of the disease and prevent resistance to therapy. Furthermore, since infliximab is approximately 25% mouse antibody, it should not be used in patients sensitive to murine proteins.

A number of adverse events have been reported with infliximab, with the more common events being infusion-related reactions and occurring in 19% of patients in clinical trials.[35,38] Reported infusion reactions include headache, fever or chills, chest pain, hypo- and hypertension, dyspnoea and injection-site reactions.[30,35,38] In order to monitor these adverse effects, it is recommended that patients are monitored for approximately 2 hours after infusion (table IV).[35] Generally, infusion-related reactions are mild and easily managed, and rarely lead to discontinuation of treatment.

The relative amount of safety information available on infliximab in psoriasis treatment is limited, as most safety data arise from its use in the treatment of rheumatoid arthritis. Thus, additional, long-term studies are required to establish its tolerability as a therapy for psoriasis.

3.1.2 Etanercept

Etanercept is a TNF-α antagonist that is currently approved in the US and Europe for the treatment of psoriasis. Unlike infliximab, etanercept is a human dimeric fusion protein; the extracellular domain of the human p75 TNF-α receptor links to the F_c portion of the human IgG1 molecule. Etanercept binds with high affinity to TNF-α and renders the bound TNF-α molecule inactive.[34]

The etanercept regimen for the treatment of psoriasis is likely to be similar to that used for psoriatic arthritis and/or rheumatoid arthritis. Etanercept is administered twice-weekly, by subcutaneous injection for 3 months, and then the dose is reduced for maintenance therapy.[39] Injections can be performed by the patient at home and etanercept

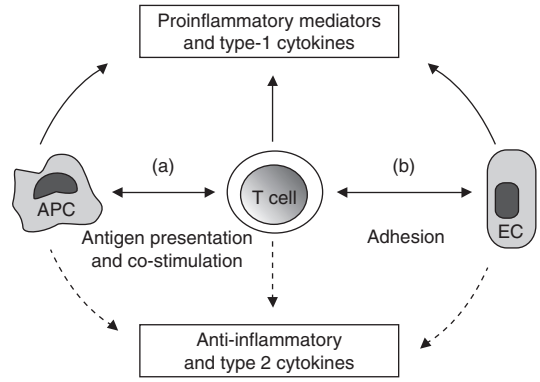

Fig. 2. Principal sites of action of the new immunomodulatory antipsoriatics. The interaction between antigen-presenting cells (APCs), T cells and endothelial cells (ECs) is involved in the pathophysiology of psoriasis. (a) The interaction between APCs and T cells can be inhibited by a blockade of antigen presentation and/or costimulation. (b) After adhesion to ECs, activated T cells migrate into the skin. Activated immune cells (including APCs, T cells and ECs) produce excessive quantities of proinflammatory mediators and type 1 cytokines, such as tumour necrosis factor-α, interleukin-2, interferon-γ and interleukin-12, which further stimulate the inflammatory reaction and are, therefore, also of pathophysiological significance. In contrast to this, the anti-inflammatory type 2 cytokines are formed in insufficient amounts. The ratio of proinflammatory to anti-inflammatory and type 1 to type 2 cytokines determines the presence or absence of the psoriatic inflammation. Thus, antagonism of the proinflammatory and type 1 cytokines or replacement by anti-inflammatory and type 2 cytokines represent new therapeutic possibilities (reproduced from Asadullah et al.,[33] with permission).

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Table IV. Monitoring required by patients receiving biological treatments for moderate-to-severe psoriasis

Timing of monitoring	Infliximab	Etanercept	Adalimumab	Alefacept	Efalizumab
Baseline	PDD and/or CXR	None	PDD and/or CXR Routine CBC/chemistries Anti-dsDNA Ab if lupus-like symptoms are present	CD4+ T lymphocyte count	Platelet count
During treatment	Infusion-related reactions 2-hours postinfusion	None	None	Weekly or biweekly[a] CD4+ T lymphocyte counts	Platelet count[b]
Patient characteristics indicating the need for special care	Pregnancy (category B) Breastfeeding Clinically important infection Pre-existing or recent onset of CNS demyelinating or seizure disorder Heart failure	Pregnancy (category B) Breastfeeding CNS demyelinating disorder History of significant haemotological abnormalities Heart failure Renal impairment Asthma	Pregnancy (category B) Breastfeeding Heart failure	Pregnancy (category B) Breastfeeding Clinically important infection History of systemic malignancy	Pregnancy (category C) Breastfeeding Clinically important infection History of malignancy

a Canada.

b More frequent upon initiation (monthly) and less frequent with continued therapy (every 3 months).

Ab = antibody; **CBC** = complete blood count; **CXR** = chest radiograph; **dsDNA** = double-stranded DNA; **PDD** = purified protein derivative.

treatment does not require monitoring before or during treatment (see table IV).

During a placebo-controlled trial in patients with psoriatic arthritis, improvements in cutaneous psoriasis were noted.[40] The median reduction in PASI was 46% for etanercept-treated patients and 8.7% for placebo-treated patients ($p = 0.0032$). Furthermore, a 75% reduction in PASI was achieved by 26% of the active treatment group while no placebo-treated patients achieved an improvement of this extent ($p = 0.0154$). An additional study reported that 32% and 46% of patients receiving 25mg and 50mg etanercept twice weekly, respectively, achieved a PASI reduction of 75%; the proportions of patients achieving this target with each of the etanercept dosages were significantly greater than the proportion of placebo-treated patients (3%; $p < 0.0001$).[41]

Etanercept has shown efficacy in patients with moderate-to-severe psoriasis, even when the dose is halved.[42] Initially, patients received a loading dosage of 50mg twice weekly for 12 weeks. For the following 12 weeks, the dose was 'stepped down' to half the dose (25mg twice weekly). Of the patients treated with the loading dose who had achieved a PASI 75 response (≥75% PASI improvement) at week 12, 77% maintained the response through to week 24 while receiving the stepped-down dose.

Long-term efficacy has also been demonstrated with etanercept; following 48 weeks' treatment with etanercept 25mg twice weekly, 67% and 38% of patients achieved PASI-50 and PASI-75, respectively.[43]

It has been estimated that the safety of etanercept can be demonstrated in >130 000 patient-years of exposure, using data from clinical trials and post-marketing experience.[44] However, most of these data have been collected from patients receiving etanercept 25mg twice weekly and there are very limited safety data for the etanercept 50mg twice weekly regimen. Further studies are required to establish the tolerability of this dose in psoriasis, and to rule out the possibility that doubling the dose will double the safety concerns over the long term.

Reports of pancytopenia (including aplastic anaemia), some with a fatal outcome, have been reported in patients treated with etanercept,[41] but

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the causal relationship to the active treatment remains unclear.

In controlled trials, several other adverse events have been reported in association with etanercept treatment; most were mild-to-moderate injection-site reactions (erythema and/or itching, pain and swelling). These occurred in approximately 37% of patients receiving etanercept, mostly during the first month of treatment.[44] Discontinuation of etanercept treatment due to adverse events was rare.

As with infliximab, little safety data are available for the specific use of etanercept in the treatment of severe psoriasis; however, it is expected that postmarketing data will be available in the future given the recent approval of etanercept for this indication in the US.

3.1.3 Adalimumab

The most recent addition to the anti-TNF-α treatment collective is adalimumab, a human recombinant IgG1 monoclonal anti-TNF-α antibody that is constructed using phage technology; adalimumab binds with high affinity and specificity to TNF-α. Since the molecule is identical to human IgG, the likelihood of immunogenicity is low;[45] however, certain monitoring procedures are required at baseline as a precautionary measure (see table IV).

When used to treat rheumatoid arthritis, for which it is approved in the US and Europe, adalimumab is administered as a single 40mg subcutaneous injection given every other week, with concurrent methotrexate therapy where indicated.

As this is a relatively novel treatment, evidence supporting the efficacy of adalimumab for the treatment of psoriasis is limited. However, Chen et al.[46] recently published preliminary findings of a 12-week, double-blind, placebo-controlled trial. When adalimumab 40mg was administered every second week, 53% of patients achieved a reduction in mean PASI score of ≥75% compared with 4% of placebo-treated patients. In addition, 80% of patients receiving 40mg every week achieved a mean reduction in PASI of ≥75%. This group also reported no significant difference between the adverse effects profiles of adalimumab and placebo.

Despite the paucity of trials and postmarketing experience on the treatment of psoriasis with adalimumab, trials have again been performed in patients with rheumatoid arthritis and so its safety profile continues to be elucidated. Abbott recently issued a warning that advised against the use of adalimumab with anakinra, an IL-1 antagonist, because of the increased risk of serious infections.[47] In addition, postmarketing experience uncovered hypersensitivity and anaphylaxis following the administration of adalimumab.[47] Although these reports concerned a patient who was receiving adalimumab for the treatment of rheumatoid arthritis, similar precautions are undoubtedly required when the drug is used to treat psoriasis. Other adverse effects, including rashes, nausea, headache and abdominal pain, have also been recorded.[45] Conversely, in other randomised control trials, there were no statistically significant differences between the adalimumab and placebo groups in their respective rates of adverse events, serious adverse events, and severe or life-threatening adverse events.[48,49]

The small number of patients treated with adalimumab, coupled with the lack of pharmacosurveillance data due to short exposure time, makes it difficult to assess the risk of the long-term tolerability of adalimumab. As a result, data regarding malignancy, demyelinating disorders and autoimmunity are limited.[50,51] Data from long-term studies and clinical practice are required to fill these gaps in the safety profile of adalimumab.

3.2 Reducing T cell Proliferation

When considering the immunological cascade of events that leads to the formation of plaques in psoriasis, an alternative opportunity for biological intervention is to reduce the proliferation of T cells.

3.2.1 Alefacept

Alefacept is a human, dimeric fusion protein containing a leucocyte function associated antigen-3 (LFA-3) region and an IgG1 region. The LFA-3 region binds to CD2, which is expressed on all T cells but is only upregulated on memory T cells, thereby preventing the LFA-3/CD2 interaction required for T cell proliferation. Alefacept also engages $F_c\gamma$ III IgG receptors on accessory cells (such as natural killer cells and macrophages) and this induces apoptosis of pathogenic T cells. To summarise, alefacept causes fewer T cells to be activated and reduces the number of active T cells. Figure 3

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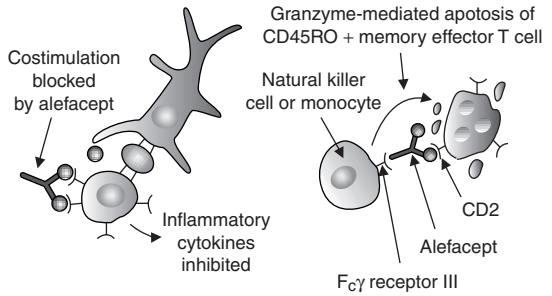

Fig. 3. Psoriasis-mediating T cells are subject to the action of alefacept, a fusion protein of the first extracellular domains of human leucocyte function associated antigen-3 (LFA-3) and the F_c portion of IgG1. Alefacept inhibits T-cell activation by blocking CD2-LFA-3 costimulation. When alefacept binds CD2 on memory effector T cells and interacts with CD16 ($F_c\gamma$ receptor III) receptors on natural killer cells and monocytes (probably in the bloodstream), granzyme-mediated apoptosis (programmed cell death) of T cells is facilitated. Because CD45RO+ memory effector T cells express more CD2 than CD45RA+ naive T cells, alefacept binds preferentially to the memory effector T cells (reproduced from Ellis et al.,[52] with permission).

schematically explains these two steps. Collectively, T cell involvement is reduced.[52]

The US FDA has approved both intramuscular (IM) and IV formulation of alefacept for the treatment of moderate-to-severe psoriasis. However, the IV formulation has subsequently been withdrawn because it is impractical for a patient to use frequent IV infusions. Alefacept is not approved in Europe. When administered intramuscularly, alefacept is given once a week, with the recommended regimen being a course of 12 weekly injections followed by a 12-week treatment-free period.

The efficacy of alefacept has been examined in a randomised, controlled trial.[53] At week 14, 21% of alefacept-treated patients achieved ≥75% reduction in PASI compared with just 5% of placebo-treated patients ($p < 0.001$). Despite these efficacy results, data on effects beyond the second 12-week course of treatment are limited. Since psoriasis is a recurrent disease, it is likely that the symptoms would eventually return during the treatment cessation period, with patients entering into a cycle of successful treatment for 12 weeks, followed by a relapse for 12 weeks that causes the patient frustration and discomfort.

The main safety concern regarding alefacept therapy is the induction of dose-dependent lymphopenia.[54] Specifically, low levels of CD4+ T cells have been reported in patients receiving alefacept. However, a recent study reported that although memory CD45RO+ T cell counts were reduced, the naive T cell population was spared.[55] As a precaution, alefacept is now contraindicated in patients with a CD4+ T cell count below normal, and regular monitoring of these lymphocyte populations is required throughout the course of treatment (see table IV). Indeed, Biogen Idec and the FDA have recently announced that because of the pathophysiology of HIV, alefacept should not be used in patients with HIV because of the effect that the treatment has on T lymphocytes.[56]

In general, alefacept appears to have a good tolerability profile. Adverse events occurring at a higher rate than with placebo included chills after the first course of treatment.[57] Although mild injection-site reactions are frequently reported,[53] patients and their physicians have not been deterred from continuing treatment.

Although the tolerability profile of alefacept appears good to date, safety data in larger numbers of patients are required and it is expected that these data will be compiled during the postmarketing period.[58]

3.3 Reducing T Cell Activation and Migration

A third immunomodulatory target for biological psoriasis therapy is to reduce the number of T cells and their migration to the epidermis.

In order for T cells to be recognised by APCs, adhesion molecules on the respective cells must interact. LFA-1 expression is increased on memory T cells and intercellular adhesion molecule-1 (ICAM-1) is its partner for adhesion, which can be found on the APC.

3.3.1 Efalizumab

Efalizumab is a humanised monoclonal antibody against the CD11a molecule. CD11a is the α subunit of LFA-1: the binding of efalizumab to CD11a on T cells blocks the interaction between LFA-1 and ICAM-1 (figure 4). T cell activation is reduced with efalizumab, and cutaneous T cell trafficking and adhesion to keratinocytes are also inhibited.[59-61]

CD11a-blockade with efalizumab is reversible and does not deplete the T cell population over

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time,[34] which would have obvious implications for immunosusceptibility and subsequent infection.

Efalizumab is the latest biological to be approved by the FDA and the EU for use in the treatment of moderate-to-severe psoriasis. In the EU specifically, it is the only biological to be approved for this indication. The compound is administered as an initial single 0.7 mg/kg subcutaneous dose, followed by weekly subcutaneous doses of 1 mg/kg.

The efficacy of efalizumab has been established in several studies.[62-67] Between 22% and 39% of patients receiving efalizumab (1 mg/kg for 12 weeks) achieved a reduction in PASI score of ≥75% compared with 4–5% of placebo-treated patients.[65-68] Furthermore, efalizumab-treated patients showed a greater improvement from baseline in PASI score than placebo as early as week 4.[65,66] It is noteworthy that efalizumab achieves these high levels of efficacy in 'high-need' patients (i.e. those for whom at least two currently available systemic therapies were unsuitable because of lack of efficacy, intolerance or contraindication).[67]

Efficacy continuing beyond 12 weeks of treatment has been reported.[69,70] In an open-label, multicentre trial, 339 patients received efalizumab 0.7 mg/kg followed by 2 mg/kg for 11 weeks. Patients were also randomised to receive either fluocinolone acetonide or placebo ointment from weeks 9 to 12.[69] Efalizumab-treated patients continued to receive 1 mg/kg from 3 months until the end of the trial. At 3 months, 41% of patients achieved a 75% improvement in PASI, while 13% achieved a 90% improvement.[69] Efficacy was maintained throughout 30 months of treatment: in the intention-to-treat population, 50% and 29% of patients maintained 75% and 90% improvements in PASI, respectively.[70] Furthermore, the mean percentage of PASI improvement at week 12, compared with baseline, was maintained at month 30.

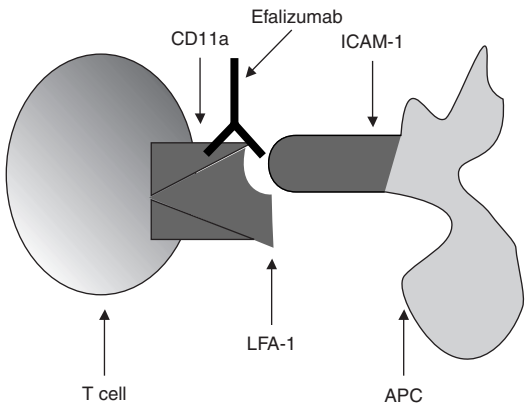

Fig. 4. The expression of the adhesion molecule, leucocyte function associated antigen-1 (LFA-1), is upregulated on memory T cells. The α-subunit of LFA-1 is CD11a. Intercellular adhesion molecule-1 (ICAM-1) is expressed on vascular endothelial cells at sites of inflammation and on keratinocytes in psoriasis. Efalizumab binds to CD11a and prevents the interaction between LFA-1 and ICAM-1. **APC** = antigen presenting cell.

With the largest safety database for any biological in psoriasis, approximately 3500 patients have now received efalizumab for psoriasis.[71] Its safety profile is beginning to emerge. Furthermore, long-term safety data are available for the use of efalizumab in the treatment of psoriasis; corresponding data are not yet available for the other biologicals. From the two phase III, placebo-controlled, 12-week trials that have been performed,[65,66] efalizumab appears to be well tolerated. Adverse events that have occurred more frequently in efalizumab-treated patients compared with placebo recipients have included headache, chills, myalgia, pain, fever, back pain and unintentional injury. These events were generally classed as mild-to-moderate in severity and decreased in frequency over time. In most cases, the adverse event rate was similar to that with placebo after the third injection. As with similar reactions to the other biologicals, these adverse events rarely caused patients to discontinue their therapy (<1%).[61]

In contrast to the regimens of other drugs in its class, there are no treatment-free periods with efalizumab, which means that treatment and thus, psoriasis control, is continuous. This regimen offers advantages over other therapies, such as alefacept (which requires a 12-week treatment-free period that is often accompanied by the return of the disease and its symptoms before patients are permitted to restart therapy). There have been some cases of relapse that have mainly occurred after discontinuation of treatment with efalizumab.[72] There appears to be a link between the responder status and incidence of relapse (i.e. patients who respond well to efalizumab treatment are less likely to experience relapse that those who do not respond as well to initial efalizumab treatment).[72] In a retrospective

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analysis, relapse occurred in 14% of all patients during a transition phase after discontinuation of efalizumab therapy. The incidence of relapse in patients who respond to treatment (achieve PASI-50 and 75) is only 6.7%.[73] Guidelines have been set to help manage patients using efalizumab therapy; if patients respond well and do not experience adverse events, they can continue with their treatment. If psoriasis events are experienced during efalizumab treatment, topical therapy can administered. If there is no clinical benefit to the patient within 12 weeks of starting the therapy, patients can be successfully transitioned to an alternative systemic therapy.[73] Inflammatory exacerbation has also been noted in approximately 1–3% of patients and mostly occurs in those who do not respond to efalizumab treatment. Again, transition to a different systemic treatment is recommended.[73]

Efalizumab has not been associated with an increased rate of infection, malignancy, hepatotoxicity or nephrotoxicity;[74] however, there have been some reports of aseptic meningitis.[68] However, as with all immunosuppressants, caution should be taken in specific patient groups in order to avoid exacerbation of latent infections or use in patients at high risk of malignancy.

To date, there have been eight reports of severe thrombocytopenia following treatment with efalizumab.[68] Analysis of pooled safety data from clinical trials reveals a slightly higher occurrence of thrombocytopenia with efalizumab treatment compared with placebo (0.3% of efalizumab-treated patients compared with no events in those treated with placebo).[75] Although most cases (six in total) were possibly drug-induced events, a number of confounding factors were present: Grave's disease, viral syndrome, drug interactions, prostate cancer and pre-existing idiopathic thrombocytopenic purpura. Causality between efalizumab and thrombocytopenia is thus yet to be confirmed; however, patients receiving efalizumab require assessment of platelet counts before treatment initiation and regularly during the course of therapy (see table IV).

4. Safety Concerns Generally Associated with Biological Therapies

4.1 Lymphomas and Other Malignancies

An increased incidence of lymphomas has been postulated to be associated with etanercept, infliximab and adalimumab treatment of patients with rheumatoid arthritis.[76] However, establishing this causal link is problematic since patients with rheumatoid arthritis have at least a 2-fold increased risk for lymphoma compared with the general population.[76-79] Furthermore, although a recent study showed increased lymphoma rates in patients receiving infliximab and etanercept therapy compared with those receiving methotrexate,[79] the authors advised caution when interpreting this finding since patients who had the highest risk of lymphoma were more likely to receive therapies such as infliximab and etanercept. While the relationship is being investigated, and since a link is biologically plausible given the mode of action of anti-TNF-α treatments, vigilance is required.

Biological therapies, in particular the infliximab, etanercept and adalimumab therapies, are also associated with an increase in malignancies in general. The risk of malignancies also appears to be higher with alefacept treatment. A randomised, controlled trial showed the incidence of malignancies following alefacept treatment was more than double that in patients receiving placebo (1.3% vs 0.5%).[54] However, it should be remembered that patients with severe psoriasis are more likely to develop malignancies, lymphomas in particular, than the general population,[80,81] thus making it difficult to attribute any increase in the rate of malignancy to one particular treatment. When using biologicals, the occurrence of malignancy could be attributed to earlier antipsoriatic therapies; this is particularly true given the time to onset of certain malignancies. Long-term safety data are required for biological therapies to confirm or refute this association.

4.2 Immunosuppression

Under normal physiological conditions, TNF-α is an important component of the immune response and, thus, administration of agents such as infliximab and etanercept will lead to immunosuppres-

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sion.[30] Increasingly, reports of serious infections such as tuberculosis (TB) have been associated with infliximab, etanercept and adalimumab therapies. In two infliximab-treated patients, the infection was fatal. Thus, caution is warranted when selecting patients for infliximab treatment. Furthermore, serious infections induced by etanercept therapy have resulted in death and have led to warnings against its use in certain patient groups.[41] As a result, screening patients for serious infections before starting treatment is advised[35] and measures should be taken to treat latent infections.[78] Further monitoring during etanercept treatment is not required following initial baseline testing (see table IV). In addition, the most common adverse events following adalimumab treatment are infections, particularly those related to the upper respiratory tract (20%), and injection-site reactions (20%).[45]

A fatal case of pulmonary non-tuberculous mycobacterial infection was recently reported in a patient receiving etanercept for rheumatoid arthritis.[82] Although no cases of TB have occurred in etanercept-treated patients during clinical trials, 20 cases of TB have occurred in patients receiving the drug. Incidentally, most of these (75%) occurred within the US.[50] In a recent review,[50] data from phase I, II and III trials indicated that the risk of reactivating latent TB was increased following treatment with adalimumab relative to controls. However, in a placebo-controlled trial, the incidence of serious infection, including TB, was similar in patients treated with adalimumab and placebo.[51] Given the evidence of an increased risk of TB with infliximab and etanercept, caution is necessary when considering a patient for adalimumab therapy. Any latent or active infections should be taken into account and all patients should be carefully monitored throughout treatment.

Of the approximately 1400 patients who have received treatment with alefacept, no clinically significant signs of immunosuppression or opportunistic infections have been observed.[34] Efalizumab is also not associated with an increased risk of TB. Most cases of serious infection associated with treatment of biologicals are because of the reactivation of latent or active infections.[78]

4.3 Demyelinating Disorders

Demyelinating disorders, such as multiple sclerosis (MS), have been reported in association with etanercept and infliximab treatment in clinical trials and also in data from postmarketing studies.[77,83] The FDA database contained cases in 19 patients: 17 following etanercept treatment and two in patients receiving infliximab infusions, with reported neurological events that were temporally related to the active treatment.[83] Although these symptoms were partly or completely resolved after treatment discontinuation, anti-TNF-α therapy should be avoided in patients with known MS or related conditions.[76]

4.4 Congestive Heart Failure

Preclinical and early clinical data suggest that TNF-α plays a role in the progression of congestive heart failure (CHF).[77] It is perhaps unsurprising, therefore, that both etanercept and infliximab treatment have been associated with not only the exacerbation of CHF, but have also been responsible for new-onset CHF (47 cases in total).[84] Trials examining a possible relationship between CHF and etanercept or infliximab treatment concluded that, at lower treatment doses, there are few/no safety issues with regards to the use of either agent; however, high dose therapy with either agent should not be initiated in patients with CHF.[85] Increased serum levels of TNF-α have been identified in patients with CHF; TNF-α may be produced as an immune response to protect the heart from the underlying disease. This may explain why treatment with the anti-TNF-α therapies (etanercept and infliximab) has been associated with the exacerbation and induction of CHF. Traditional treatments and other biological therapies, such as efalizumab and alefacept, have not been associated with these adverse events.

5. Summary and Conclusions

Psoriasis is a chronic, inflammatory condition of the skin and appears to be a T cell-mediated disease. There are a number of traditional systemic therapies available for the treatment of moderate-to-severe psoriasis, including methotrexate, ciclosporin, oral retinoids, UV and PUVA therapy, and fumaric acid esters. Although limited by their toxic thresholds,

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traditional systemic treatments still have an important place in the antipsoriatic armamentarium.

Many traditional systemic treatments are associated with frequent, serious adverse effects, such as serious infections, organ failure and malignancies. These adverse effects can make such therapy difficult to justify in a disease such as psoriasis, and in some cases necessitate intrusive monitoring procedures. Adverse effects may also force intermittent use of the therapy, which, in turn, complicates the assessment of remission rates and risks reappearance of psoriatic symptoms. The toxic threshold of the more traditional treatments for psoriasis has prompted further investigation into novel therapeutic targets for psoriasis. A better understanding of the immunological basis of the condition, coupled with biotechnological advances, has facilitated the development of biological therapy.

Biological therapy, initially used for the treatment of autoimmune diseases such as rheumatoid arthritis and Crohn's disease, has been revealed to be effective in the treatment of moderate-to-severe psoriasis. Infliximab, etanercept and adalimumab all target TNF-α, which is a proinflammatory cytokine. Other agents interact with T cells: alefacept reduces the number of active T cells, while efalizumab prevents T cell activation, trafficking and adhesion to keratinocytes. The mechanism of action of biological therapies allows the targeting of the underlying cause of the disease, rather than just the treatment of symptoms. As a result, their efficacy is remarkable and does not compromise safety or tolerability. In addition, a recent review has compared patient satisfaction with the currently available treatments for psoriasis[71] and concluded that the encouraging efficacy, safety and simplified treatment regimens offered by the biologicals will improve patient satisfaction with psoriasis treatment. That said, some concerns regarding biological therapy-induced adverse effects have been raised.

Early biological treatments, while being more effective and tolerable than the traditional systemic agents, still have safety limitations and induce injection-site reactions. In particular, the incidence of serious infection appears to be higher in patients receiving biological therapy compared with the general population. There are issues with patients developing antibodies towards infliximab, which reduces its efficacy; etanercept has been associated with increased risk of TB, CHF and demyelinating disorders. As research continues to progress, the immune targets for such treatments will become increasingly specific with the intention of minimising adverse effects. To date, it appears that efalizumab is one of the more tolerable biological treatments, in both the short term and the long term, as it has a good safety profile with good efficacy. Thrombocytopenia has been reported in 0.3% of treated patients,[75] yet efalizumab is unique among other biologicals as it is the only agent in its class showing both efficacy and safety over 2.5 years of continuous treatment.

Acknowledgements

Professor Shear has received no direct payments towards the preparation of this manuscript. He has been a paid consultant, clinical trialist and received educational support from pharmaceutical manufacturers that make and market systemic therapies for psoriasis (including Abbott, Amgen, Biogen, Idec, Centocor, Hoffmann LaRoche, Genentech, Novartis, Schering Canada, Serono, Wyeth and Xoma).

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