Biological therapy for psoriasis

Psoriasis is a common, chronic immune-mediated skin disorder. Recent advances in the understanding of the immunopathogenesis of psoriasis have led to the development of biological agents designed to target the molecular mechanisms of the condition. These provide new and effective treatments for patients with moderate to severe psoriasis.

Psoriasis is a chronic but treatable immune-mediated skin condition affecting 2% of the UK population and an estimated 80 million people worldwide (Griffiths et al, 2004). Current systemic therapies (e.g. methotrexate and cyclosporin) for patients affected by moderate to severe disease are well established and have good efficacy in most cases. However, they have associated toxic side-effects and treatment-resistant disease in a proportion of patients is a significant problem. Recent advances in the knowledge of the pathogenesis of psoriasis has enabled new biological agents, known as biologics, to be developed, which offer an exciting and optimistic approach to treatment for patients affected by unremitting disease.

Clinical aspects

The most common form of the disease is chronic plaque psoriasis, which occurs in around 85% of patients (Griffiths et al, 2004). This is manifest as thick, red and heavily scaled plaques, usually present on the extensor aspects of the limbs, lower back and scalp, although any skin surface may be affected (*Figure 1*). The psoriasis area and severity index (PASI) (Fredricksson and Petterson, 1978) is used to determine severity by assessing the skin surface area involved by psoriasis and the degree of redness, induration and desquamation of the plaques. Other variants include guttate, flexural, erythrodermic and generalized pustular psoriasis, although these subtypes are encountered less frequently. Nail dystrophy is common and includes pitting, onycholysis and subungal hypertrophy. In addition, 5–10% of patients have an associated inflammatory seronegative arthritis known as psoriatic arthritis (Griffiths et al, 2004). Most patients develop psoriasis before 40 years of age and often disease is familial.

As with most chronic conditions, the course of psoriasis is variable with intermittent relapse and remission, and while psoriasis is not typically life-threatening, it can greatly affect a person's appearance, self-esteem and overall quality of life. In fact, studies have shown that psoriasis imparts a negative effect on a patient's quality of life equivalent to that seen in conditions such as cancer, arthritis and heart disease (Rapp et al, 1999; Kirby et al, 2001; Choi and Koo, 2003; Sampogna et al, 2004; Stern et al, 2004).

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Immunology of psoriasis

Psoriasis is one of the most prevalent T-cell mediated inflammatory disease in humans. The histopathology of a psoriatic plaque is characterized by epidermal keratinocyte hyperproliferation, loss of differentiation, angiogenesis and an inflammatory infiltrate consisting predominantly of T lymphocytes. Specific T cells secrete TH1 cytokines including interferon-γ and interleukin-2 which stimulate the subsequent production of chemokines, granulocyte-macrophage colony stimulating factor and epidermal growth factor. The pro-inflammatory cytokine tumour necrosis factor-α (TNF-α) is an important and highly active component of this inflammatory infiltrate (Griffiths, 2003) and has been shown to be a major factor in the pathogenesis of both psoriasis and psoriatic arthritis.

Figure 1. Extensive plaque psoriasis consistent with severe disease.

Current treatment of psoriasis

There are a number of treatment options currently available for patients with psoriasis depending on the type, site and severity of disease. Topical treatments are usually adequate for the majority (75%) of patients and include emollients, topical corticosteroids, coal tar preparations, vitamin D3 analogues, dithranol and salicylic acid (Lebwohl and Ali, 2001). For the 20–30% of patients with moderate to severe forms of the disease, the conventional systemic treatments such as methotrexate, cyclosporin, acitretin (an oral retinoid) and phototherapy, and photochemotherapy psoralens and ultraviolet A (PUVA) have been the mainstay of treatment until recent years.

Unfortunately, each systemic treatment can be associated with various toxic side-effects and there are a proportion of patients who are either unsuitable for these therapies and/or whose disease remains treatment-resistant (Griffiths et al, 2000).

What are biological therapies?

Most medicines are manufactured by combining chemicals. In contrast, biological therapies or biologics are made from proteins derived from living material – human, plant, animal or microorganism. They are designed to target specific molecular steps that cause disease and have already been shown to be effective in a variety of autoimmune diseases such as rheumatoid arthritis and Crohn's disease. They possess pharmacological activity and can be manufactured in considerable quantities using recombinant DNA techniques. They are not entirely new treatments as they have been in use for close to 100 years, examples including insulin and certain vaccines.

Currently, biological therapies for psoriasis comprise two main groups:

- Agents targeting T cells or antigen-presenting cells (efalizumab, alefacept)
- Agents targeting the cytokine TNF-α (etanercept; infliximab, adalimumab).

Three of these, efalizumab, etanercept and infliximab, are licensed in the UK for patients with moderate to severe psoriasis. These three agents will therefore be discussed in further detail.

T-cell targeted biologicals

Efalizumab

Efalizumab is a recombinant, humanized monoclonal antibody to CD11a, the α subunit of leucocyte function-associated antigen (LFA-1), a cell surface adhesion molecule important in T-cell activation, mediated by the binding of LFA-1 and intercellular adhesion molecule-1 (ICAM-1). This ligand-ligand receptor adhesion is blocked by efalizumab, resulting in inhibition of T-cell activation, and adhesion of circulating T cells to ICAM-1-expressing dermal endothelial cells, inhibiting cutaneous T-cell trafficking.

Administration:

- Once-weekly self-administered subcutaneous (sc) injection
- Conditioning dose of 0.7 mg/kg
- Standard 1 mg/kg dose, may be used continuously.

Response rates: Efalizumab appears to be effective in chronic plaque psoriasis with 27% of patients achieving a PASI 75 (i.e. 75% reduction in PASI score) response by week 12 and 44% of patients at week 24 (Menter et al, 2005). Only those patients who respond at 12 weeks can continue treatment and there is evidence that efalizumab may be used as a safe maintenance therapy for up to 5 years.

Adverse effects: Flu-like symptoms are the most common side-effect to occur initially, although this usually settles after 3–4 weeks of treatment (Leonardi et al, 2005; Menter et al, 2005). At a later stage, between 4 and 10 weeks, patients may develop a transient pruritic skin eruption that is self-limiting and should be treated with topical steroids. Thrombocytopenia is a rare side-effect, but it is therefore necessary to monitor platelet counts throughout the course of treatment.

As with all biological agents, there is considerable concern regarding increased risk of infection and malignancy. However, there is no statistical evidence, to date, to suggest that efalizumab results in an increased risk of either serious infection or malignancy.

TNF-α inhibitors

Infliximab

Infliximab is a monoclonal, mouse-human chimeric antibody with a high binding affinity and specificity for TNF-α. In the UK it is licensed for treatment of rheumatoid arthritis, fistulating Crohn's disease, ankylosing spondylitis and psoriasis. It is the most widely used biological agent in dermatology clinical practice today.

Administration:

- Intravenous infusion over 2 hours
- 5 mg/kg at weeks 0, 2 and 6
- Maintenance infusions at 8-weekly intervals.

Response rates: Infliximab produces a prompt and marked improvement in the majority of patients. Initial response is usually observed between 2 and 4 weeks, and by 10 weeks 87% of patients have achieved PASI 75. A study by Reich et al (2005) has demonstrated that infliximab is good for maintaining improvement for 1 year and produces significant benefit for psoriatic nail disease. It has also been shown to be highly effective for patients with psoriatic arthritis. It is paramount, however, to compare the risks associated with maintenance infusions with the risk of disease deterioration.

Etanercept

Etanercept is a human recombinant TNF receptor p75 fusion protein that imitates naturally occurring TNF-α receptors. It binds TNF-α with high affinity and specificity, subsequently inhibiting its pro-inflammatory effects.

It has already been used for a number of years to treat inflammatory arthritis.

Administration:

- Self-administered sc injection
- 50 mg twice weekly initially
- 25 mg twice weekly according to individual patient response
- Approved for 24 weeks continuous therapy.

Response rates: Studies have shown that etanercept is effective in patients with moderate to severe chronic plaque psoriasis (Mease et al, 2000; Gottlieb et al, 2003; Leonardi et al, 2003). Improvement is dose dependent, with 34% of patients on 25 mg twice-weekly injections achieving PASI 75 at 12 weeks, compared to 49% of patients on 50 mg twice-weekly injections. Continued treatment provides further benefit at 24 weeks. Treatment response in severe unstable disease and in erythrodermic or generalized pustular psoriasis is not yet established. As with infliximab, etanercept is effective in the treatment of psoriatic arthritis.

Adverse effects: The most frequently observed side-effect with etanercept is a self-limiting injection site reaction. This affects between 10–20% of patients, usually in the first few weeks, and resolves spontaneously (Zeltser et al, 2001). A more serious infusion reaction may occur with infliximab in around 20% of patients, requiring treatment with antihistamine and hydrocortisone. Anaphylaxis can occur, although this is a rare event.

Patients can develop antibodies to etanercept or infliximab although data on this are still limited for patients with psoriasis. There is an increased risk of reactivation of tuberculosis especially with infliximab (Keane et al, 2001; Lim et al, 2002). Any patient with active tuberculosis should therefore receive anti-tuberculosis treatment before commencing anti-TNF therapy. Anti-TNF therapy may cause exacerbation of moderate to severe congestive cardiac failure (Kwon et al, 2003) and it should therefore be avoided in these patients. Treatment with infliximab and etanercept is contraindicated in patients with demyelinating disease or optic neuritis.

KEY POINTS

- Psoriasis is a common T-cell mediated inflammatory disease.
- Between 20 and 30% of patients have moderate to severe disease requiring systemic therapy.
- Conventional systemic therapies are limited by organ toxicity.
- Biological therapies are proteins derived from living material that target specific molecular steps that cause disease.
- Biological therapies for psoriasis target T cells (efalizumab) or the cytokine TNF-α (etanercept, infliximab).
- These significant developments in clinical dermatology offer a new and effective treatment approach with the potential for safe, prolonged control of symptoms for patients with moderate to severe chronic plaque psoriasis.

Assessment and monitoring: Suitability for biological therapies for psoriasis is subject to strict criteria including PASI ≥10, significant impairment of quality of life and non-response to or unsuitability for traditional systemic therapies. Before commencing treatment, all patients require a thorough clinical history, haematology and biochemistry laboratory investigations, and screening for hepatitis B and C and human immunodeficiency virus (HIV) infection in high-risk patients. For patients starting anti-TNF therapy, screening for active tuberculosis is recommended. The British Association of Dermatologists has published guidelines on the use of biological therapies for psoriasis (Smith et al, 2005).

At 12 weeks of treatment with a biological therapy, all patients should be reviewed to ascertain whether this treatment should continue. An adequate response is measured by a 50% or more improvement in PASI and at least a five point improvement in the dermatology life quality index (Ashcroft et al, 1999; Lewis and Finlay, 2004). Those patients not achieving an adequate response or who develop an adverse side-effect should discontinue treatment.

Conclusions

Biological therapies have been used for several years and have produced beneficial results for patients with various autoimmune conditions such as inflammatory arthritis and Crohn's disease. They have emerged as a relatively new concept in clinical dermatology, although studies to date have provided sufficient evidence to confirm their effectiveness for patients with moderate to severe forms of chronic plaque psoriasis. Further clinical trials will be necessary to further evaluate specific treatment regimens and, along with a national patient register, determine their longer-term efficacy and safety profile. **BJHM**

Conflict of interest: Professor CEM Griffiths is a paid consultant to and has received research grants from Serono, Wyeth and Schering Plough, the manufacturers of efalizumab, etanercept and infliximab respectively.

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