Current and potential new therapies for the treatment of psoriasis

In our latest article on science, Adam Todd, Roz J. Anderson, Paul W. Groundwater and Suja Elizabeth George look at current treatments for psoriasis, discuss scopes for new therapies and look at some new agents in development.

The word *psora* comes from the Greek, meaning "to itch". Psoriasis, a term which has been in use since c 133 AD, was originally grouped with leprosy until the 19th century. It has been suggested that biblical leprosy was, in fact, the disorder known today as psoriasis. In 1881, Thin described psoriasis as "a disease of the skin, in which white masses of epidermic scales are attached, more or less firmly to a reddish vascular base. When the scales are removed by the finger nails, small drops of blood ooze from the vascular surface". The condition described by Thin is clearly the disease recognised today as psoriasis vulgaris, or plaque psoriasis, the most common form of the condition, constituting around 80 per cent of cases and affecting the scalp, elbows, knees and lumbar region of the back, all of which have a high epidermal turnover. The classical features of this disorder are chronic erythematous plaques covered with silvery scales. Thin also recognised that inflammation of the epithelium is a key characteristic of psoriasis.

The relatively few population-based studies that have investigated the prevalence of psoriasis estimate that it affects around 2 per cent of the global population, with ethnic factors playing a role. Gender does not seem to affect the prevalence of psoriasis, with similar rates reported in men and women, while patients affected by Crohn’s disease, another chronic inflammatory disorder, are greater than three times more likely to suffer from psoriasis.

Treatments

Current treatments for psoriasis fall into three major categories: topical, ultraviolet light (phototherapy) and systemic.

Topical therapies

Topical lotions, ointments, creams, gels, and shampoos for the skin and scalp are prescribed for mild to moderate cases of psoriasis or, in combination with other treatments, for more severe cases. Topical agents used to treat psoriasis include vitamin D analogues (eg, calcipotriol), corticosteroids, retinoids (eg, tazarotene), dithranol and coal tar products. These drugs slow skin-cell production and reduce inflammation (except dithranol, which is known to generate free radicals, although, despite many years of use, its exact mechanism of action is still unclear).

Light therapy

Light therapy usually involves exposure to a short wavelength of ultraviolet light, called UVB. In the case of resistant moderate to severe psoriasis, a combination of oral or topical psoralen and a photosensitising agent, the US Food and Drug Administration and the European Medicines Agency have recently notified healthcare professionals of the voluntary, phased withdrawal of efalizumab. Efalizumab is a recombinant humanized monoclonal antibody that targets the lymphocyte function-associated antigen-1 (LFA-1)/inter-cellular adhesion molecule-1 (ICAM-1) interaction, which is involved in the regulation of immune cells. The next biological agent, etanercept, competitively binds to TNF-α receptors on the cell surface. Although infliximab and etanercept have different mechanisms of action, they produce the same pharmacological outcome (ie, they inhibit the action of TNF-α).

Systemic treatments

Systemic treatments include both orally and parenterally administered agents for the treatment of psoriasis that is severe, resistant or complicated. Systemic drugs that may be prescribed for psoriasis include methotrexate, ciclosporin and the biologics.

Biologics

Over the past few years, an understanding of the immunopathological mechanisms that occur in psoriasis has been elucidated. Indeed, few disorders highlight the complex interactions between cytokines and chemokines in the initiation and maintenance of chronic inflammation as clearly as psoriasis. This has enabled the development of therapies specifically targeted at inhibiting pathogenic T-cells (lymphocytes that play an important role in cell-mediated immunity), or at blocking cytokines they secrete.

Biologics, which target the underlying immunopathogenesis of psoriasis, have been released onto the market relatively recently. Infliximab is a humanised monoclonal antibody that inhibits the actions of tumour necrosis factor-α (TNF-α), which is involved in the regulation of immune cells. The next biological agent, etanercept, competitively binds to TNF-α, preventing it from binding to TNF-α receptors on the cell surface. Although infliximab and etanercept have different mechanisms of action, they produce the same pharmacological outcome (ie, they inhibit the action of TNF-α).

Despite the success of the biological agents, the US Food and Drug Administration and the European Medicines Agency have recently notified healthcare professionals of the voluntary, phased withdrawal of efalizumab. Efalizumab is a recombinant humanised monoclonal antibody that targets the lymphocyte function-associated antigen-1 (LFA-1)/inter-cellular adhesion molecule-1 (ICAM-1) interaction, which is involved in T-cell activation and recruitment to the site of infection. Efalizumab, which was originally approved for the treatment of severe plaque psoriasis, has been withdrawn from the US and European markets due to a potential risk to patients of developing progressive multifocal leukoencephalopathy (PML). PML is a viral disease that is usually fatal, which occurs almost exclusively in patients with severely impaired immunity. 

Plaque psoriasis is the most common form of psoriasis and constitutes around 80 per cent of cases.

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compromised immune systems and is characterised by inflammation of the white matter of the brain at multiple locations.

Despite these problems, the biology of treating severe forms of psoriasis, Most topical products available have a role in the management of mild to moderate plaque psoriasis, but remain ineffective for severe plaque psoriasis. The systemic products available for the treatment of severe forms of psoriasis can have serious adverse effects and should only be initiated under specialist supervision. For example, methotrexate and ciclosporin cause blood dyscrasias and nephrotoxicity, respectively, while phototherapy can increase the risk of developing skin cancer. For the corticosteroids and dithranol, which have been in use for more than 50 years, the risks are well known, but the long-term side effects of newer drugs, such as the biologicals, are unknown, and can lead to product withdrawal due to serious side effects (as was the case for efalizumab).

These newer biological agents can be successful in managing severe forms of this disease, but a major disadvantage is that, due to their high molecular weight, they have to be administered via the parenteral route, which can be a major inconvenience to the patient.

In view of the problems with the biological agents and the toxicity associated with the systemic products, there still remains a distinctive need for a new chemical entity with the ability to treat severe forms of psoriasis, so many research groups have focused their attention on the underlying mechanisms of psoriasis and the potential for the treatment of severe forms of the disease. There are many examples of compounds that have been patented to treat psoriasis and remain under development, some of which are discussed below.

Scope for new therapies
It has been many years since a new chemical entity has been discovered for the treatment of psoriasis. Most topical products available have a role in the management of mild to moderate plaque psoriasis, but remain ineffective for severe plaque psoriasis. The systemic products available for the treatment of severe forms of psoriasis can have serious adverse effects and should only be initiated under specialist supervision. For example, methotrexate and ciclosporin cause blood dyscrasias and nephrotoxicity, respectively, while phototherapy can increase the risk of developing skin cancer. For the corticosteroids and dithranol, which have been in use for more than 50 years, the risks are well known, but the long-term side effects of newer drugs, such as the biologicals, are unknown, and can lead to product withdrawal due to serious side effects (as was the case for efalizumab).

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ISA247 ISA247 (also known as voclosporin) is an analogue of ciclosporin and is being developed by the biopharmaceutical company Isotechnika. ISA247 is a next generation calcineurin inhibitor and, when administered orally, is safe and effective in the treatment of moderate to severe plaque psoriasis, as shown in a recently published phase III trial. Furthermore, the results from the recent ESSENCE trial show that voclosporin demonstrated good efficacy compared with placebo and showed fewer adverse effects than ciclosporin, which is a major advantage.

A new drug application for ISA247 has recently been accepted for priority review by the FDA, which accelerates the review period to six months.

Bz-423 Bz-423, a 1,4-benzodiazepine, chemically related to the anxiolytic diazepam, has also been patented for the treatment of psoriasis (see figure). The development of Bz-423 is not as advanced as that of ISA247, but it has shown promise in in vivo and in vitro tests. Indeed, Bz-423 has been shown to suppress keratinocyte proliferation (a key feature of psoriasis) in a murine model. Bz-423 also promotes cell death and is thought to target the Fp=ATPase, inducing the formation of superoxide (a reactive oxygen species) that initiates cell death through a complex signaling pathway.

Conclusion
The ability to develop novel treatments for psoriasis by rational design is dependent on our understanding of the immunopathological mechanisms behind psoriasis. Clearly, a great deal of progress has been made since Thin’s paper in 1881, which has resulted in more effective therapies being discovered, but further work is needed to find new agents to continue the progress against this debilitating disease.

References
10. New drug application for voclosporin accepted for priority review by FDA. Available at: www.isotechnika.com (accessed 21 May 2010).

Figure 1: The chemical structures of Bz-423 (top) and diazepam (bottom)