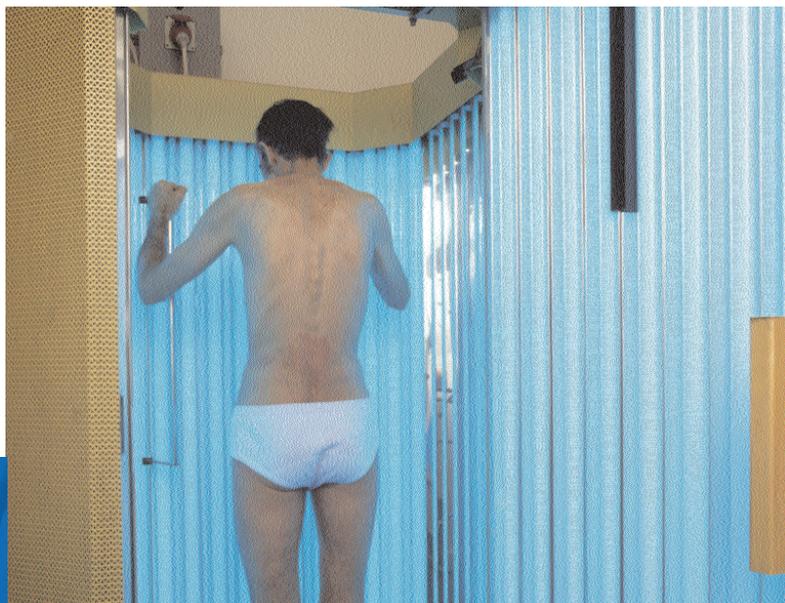


Management of severe psoriasis

In this second article on psoriasis, **Christine Clark** looks at phototherapy and systemic therapy



St Bartholomew's Hospital/SPL

UV radiation therapy is used for psoriasis

Topical treatments may not be sufficient for patients with moderate to severe psoriasis and further options include photo- or systemic therapy. Although these treatments are usually prescribed and managed by hospital-based specialists, it is important for all pharmacists to be aware of them and to have an understanding of their implications for patient care. Potential drug-drug interactions, drug-phototherapy interactions and early identification of serious side effects are all issues that need to be considered.

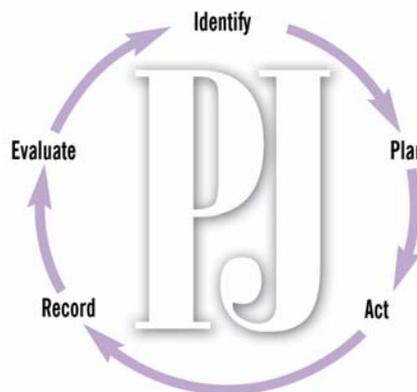
Immunological basis of psoriasis

Psoriasis is now thought to be a disease in which chronic T-cell activation (see Panel 1, p690) by antigen-presenting cells occurs in the skin (ie, it is an immune-mediated disease). Once activated, the T-cells express the inflammatory cytokines TNF- α and interferon- γ . These trigger changes in keratinocyte function and epidermal hyperproliferation as well as a variety of inflammatory responses, including:

- Release of vascular endothelial growth factor (causing angiogenesis and increased vascular permeability)
- Release of further pro-inflammatory cytokines and attraction of neutrophils

The trigger antigen has not yet been identified and new approaches to treatment have focused on drugs that can block T-cell activation, migration or cytokine secretion. The immunological explanation of psoriasis also helps us to understand how the systemic agents might exert their actions.

Some people with psoriasis also have an associated arthropathy. Between 10 and 23



Identify knowledge gaps

1. What is PUVA?
2. What factors need to be considered when dispensing methotrexate?
3. Which drugs for psoriasis are being reviewed by the National Institute for Clinical Excellence?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "common disease states" (see appendix 4 of "Plan and record").

per cent develop joint inflammation (psoriatic arthritis).

Phototherapy and photochemotherapy

The beneficial effects of sunlight in psoriasis have been known for centuries. Treatment with artificial UVB radiation was introduced early in the 20th century and this was later followed by PUVA (psoralen plus UVA) in the 1970s. Both UVB and PUVA are thought to modulate the expression of cellular adhesion molecules and induce T-cell apoptosis (programmed cell death). Phototherapy is suitable as first line treatment for patients with extensive, small plaque psoriasis and for those whose disease has failed to respond to topical treatment.

UVB UVB is light of wavelengths 290–320nm. It is the part of the absorption spectrum that is responsible for sunburn. Originally UVB was used in combination with coal tar) but, more recently, it has been used alone. Because UVB burns, the dose (exposure time) has to be adjusted (through a series of tests) to match the skin type of the patient.

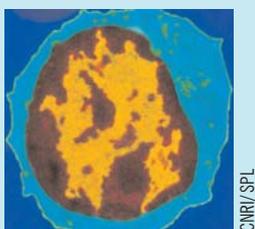
The "minimum erythemogenic dose" (MED; the minimum dose of UVB that causes perceptible faint pinkness of skin 24 hours after irradiation) is established, and a reduced dose (usually 80 per cent of the MED) is then given three times a week until the psoriasis

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Panel 1: T-cell activation

T-cells are white blood cells critical to the immune response. Among these are CD4+ T cells and CD8+ T cells. The "T" stands for the thymus, where T lymphocytes mature.

In psoriasis, the activation of T-cells involves two critical steps. First, the T-cell binds to an antigen-presenting cell (APC) through an interaction between surface proteins on each cell (the integrin, LFA-1 on the T-cell surface and the adhesion molecule ICAM-1 on the APC). This stimulates the first signal. To bring about T-cell activation, a second, co-stimulatory signal is required. This occurs through binding of several pairs of ligands on the surfaces of the two cell types. Activated T-cells migrate to the skin where they cells stimulate keratinocytes to behave untypically.



clears. This usually takes four to six weeks. Each treatment takes only a few minutes.

Antipsoriatic activity appears to be associated with the wavelengths 300–313 nm and this led to the introduction of "narrow band" UVB, using lamps that produce mainly 311nm \pm 2nm wavelengths. The removal of the shorter wavelengths reduces the risk of burning.

Male patients receiving UVB treatment have an increased risk of developing tumours in genital skin and for this reason the genitals should be covered during treatment. The risks of non-melanoma skin cancer with UVB are as yet unknown.

UVB therapy is contraindicated in patients who are taking photosensitising medicines (eg, thiazide diuretics or tetracyclines) and in patients with underlying photosensitive diseases (eg, systemic lupus erythematosus, polymorphous light eruption).

PUVA Ultraviolet A is light of wavelengths 320–400nm. It penetrates deeper into the skin than UVB but has little action on its own. When given together with a psoralen photosensitiser the effects of UVA are greatly enhanced. The UVA induces a phototoxic reaction that causes the psoralen to form cross links between complementary strands of DNA, causing cell death. The most commonly used sensitiser is 8-methoxypsoralen (8-MOP), which is available in tablets, lotion, paint or as a bath solution. It is important to ensure that the psoralen is present in the skin at the time that the UVA is given. Oral 8-MOP is given one to two hours before irradiation and topical psoralens are applied immediately before irradiation. The UVA dose is usually determined by an assessment of skin type (eg, type I always burns and never tans,

type IV never burns and always tans) rather than by patch testing.

One drawback of the oral treatment is that the patient remains photosensitive until the psoralen has cleared from the body (12 to 24 hours). These patients are vulnerable to the effects of natural sunlight and need to protect their skin. In order to minimise the risk of cataract formation they are also advised to wear dark glasses during this time. Some patients experience nausea with the psoralen. PUVA treatment is given twice a week until the psoriasis clears.

Prolonged exposure to PUVA is associated with an increased risk of non-melanoma skin cancer and photo-ageing of the skin. As with natural sunlight, fair-skinned individuals are more susceptible to these effects. The British Photodermatology Group has recommended that the maximum lifetime exposure to UVA should be less than 1000J/cm² or 250 treatments but unless meticulous records are kept it is easy for this limit to be exceeded.

Excimer laser Recently, a number of studies have been conducted using UVB light from an excimer ("excited dimer") laser. Excimer lasers are characterised by short wavelengths, high intensities and short pulse durations. Unlike conventional lasers they do not generate heat, which could damage surrounding tissue. Moreover, treatment times are shorter than with traditional UVB and the light can be directed at the affected areas. Excimer laser treatment may, in the future, be an option for faster treatment of isolated lesions but it is not yet widely available.

Systemic therapy

Systemic therapy for psoriasis includes oral methotrexate and ciclosporin. Other drugs that affect the immune response, for example, hydroxycarbamide, etanercept and infliximab are sometimes used, but these are not licensed for psoriasis.

Methotrexate The dihydrofolate reductase inhibitor methotrexate interferes with DNA synthesis by preventing the formation of tetrahydrofolate. Methotrexate has been used for many years in the treatment of malignant disease but it is also used, in much lower doses, in the management of psoriasis. Its action was presumed to be immunosuppressive and studies have shown that methotrexate inhibits other enzymes, causing adenosine, a T-cell toxin, to accumulate. This may account for its immunosuppressive activity.

Methotrexate is indicated for the treatment of severe, recalcitrant psoriasis so is only used in a small number of psoriasis sufferers. It is given in a single weekly dose of 12.5–20mg, and it is used both for clearance of disease (it can clear psoriasis in eight weeks) and for maintenance. It should not be given to people with active infections or during pregnancy or lactation. Methotrexate also inhibits spermatogenesis and should not be given to men who wish to father children. The azoospermia is reversible but a wash-out period is required.

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A pharmacist-patient view

My psoriasis started about eight years ago, when I was 25. The most common features for me are plaques on my elbows and scalp psoriasis. The scalp disease is the most troublesome. I get thick plaques, about 3–4 inches across with hair growing through them. The plaques shed scales in a big way. It is not like normal dandruff because the flakes of skin are bigger and thicker and the condition does not respond to ketoconazole shampoo. It does not itch but it is irritating and makes me want to scratch. But if I do scratch, or brush my hair, silvery flakes almost like mica crystals, up to 0.5cm across fall out in a shower. The skin underneath the scales is red and sore. I find that all scalp applications for psoriasis work but they sting terribly, especially if I have been scratching. I usually use betamethasone scalp application. I get psoriasis inside my ears too, but this responds to a dab of scalp lotion. When the plaques on my elbows flare up, I treat them for a couple of weeks with steroid cream until they are small and pale enough for them not to bother me.

The worst thing of all is flexural psoriasis. I have had three or four outbreaks. A couple of times it has been misdiagnosed as intertrigo (candidal) and treated with antifungals. I get it under the breasts and in the groin. It looks red and raw — a bit like nappy rash. If you let it dry out, it looks a bit silvery. Actually, the worst part is chafing of underwear and when you go swimming it is embarrassing if it extends beyond the edge of the swimsuit. Taking showers at the gym is embarrassing too so I usually avoid these activities if it is bad. I get self-conscious if the psoriasis is where people can see it. The worst part is shedding skin scales — you get a snowstorm effect, which is visible on dark clothing.

My hairdresser knows about my psoriasis but if I go somewhere new I feel that I have to explain in case they think it is contagious. I use Capasal shampoo to remove the scales, followed by a nice-smelling shampoo, because I do not want to smell of coal tar. If my scalp is flaring up, I wet the hair then rub Capasal into scalp and leave it for five minutes before washing it out. This helps to remove the scale.

I do not use coal tar products — I do not like the smell — and they are less effective than steroids, so I keep a tube of Betnovate cream handy. I only use it for a few days to get the psoriasis under control. I also keep Betnovate Scalp Application. I have tried calcipotriol on my scalp but it did not work as well as betamethasone. I use emollients too, especially on my elbows. I have tried lots but found Unguentum Merck is best for me. I also use white soft paraffin on dry parts. It is effective but I can only use it at night when it does not matter if I am sticky.

A test dose is normally given before regular treatment is started to check that the patient is not unusually sensitive to the immunosuppressive effects. Regular monitoring for signs of bone marrow suppression and the development of liver fibrosis is essential during methotrexate treatment. Patients must be advised to look out for signs of infection (eg, sore throat), which could be the result of bone marrow suppression. Avoidance of alcohol is recommended to minimise the risks of liver damage.

Nausea is the most common side effect. It usually starts within 12 hours of taking the dose and can persist for up to three days. Folic acid, in a dose of 5mg daily, has been found to be more helpful than conventional antiemetics. Other side effects of methotrexate include mucosal ulceration, stomatitis, macrocytic anaemia and pneumonitis.

Accidental over-dose has been a serious risk for people taking weekly doses of methotrexate. The National Patient Safety Agency has published a patient safety alert setting out the steps that need to be taken by health care professionals to ensure that methotrexate is used safely. Methotrexate is cleared by the kidneys, so drugs such as some penicillins, salicylates, non-steroidal anti-inflammatory drugs and probenecid can reduce clearance and increase toxicity.

Although methotrexate has been used

since the 1950s, the treatment success rate is uncertain — only one randomised control trial has been performed. However, dermatologists view this treatment as effective.

Ciclosporin Ciclosporin has been used for many years as an immunosuppressant in organ transplantation. In the late 1970s its beneficial effects in psoriasis were recognised. Ciclosporin blocks the intracellular components of T-cell activation through a series of interactions resulting in inhibition of calcineurin phosphatase, which in turn inhibits nuclear factor of activated T-cells. This regulates production of T-cell cytokines.

Ciclosporin in doses of 2.5–5.0mg/kg can clear psoriasis in six to eight weeks. It is indicated for severe psoriasis. It is sometimes used for maintenance treatment but the risks of side effects are often thought to outweigh the benefits. Ciclosporin is contraindicated in pregnancy and breast-feeding and should not be given to people who are immunosuppressed. The most common side effects are mild nausea and indigestion. The most serious side effects are nephrotoxicity and hypertension. Both are dose dependent and of gradual onset.

Regular monitoring of renal function using serum creatinine levels is essential. If the level rises to 130 per cent of the baseline level then the ciclosporin dose should be reduced or treatment discontinued. Moderate hypertension can be treated with nifedipine. Other side effects include hypertrichosis and neurological events such as dysaesthesiae (abnormal sensations of the skin, typically pins and needles), tremors and headaches. In spite of its immunosuppressive activity, the use of ciclosporin in dermatology does not appear to cause internal malignancies or increased susceptibility to infection.

Ciclosporin is metabolised via CYP3A (cytochrome p450 3A) and mainly excreted in the bile. Numerous drugs interact with ciclosporin to raise or lower blood levels, and put the patient at risk of increased toxicity or decreased effect. One commonly seen interaction is when erythromycin is prescribed, causing ciclosporin levels to rise, often with beneficial effect on the psoriasis causing the patient to assume that erythromycin is good for psoriasis.

Systemic retinoids Retinoids are vitamin A analogues. They bind to nuclear receptors that regulate gene transcription. In psoriasis they induce keratinocyte differentiation and reduce epidermal hyperplasia. Etretinate and its metabolite acitretin have both been used in the treatment of psoriasis. The major limitation to their use is their teratogenicity (hence the withdrawal of etretinate). Etretinate is deposited in body fat and has a half-life up to 120 days. Acitretin is less lipophilic and has a shorter body half-life but a portion of the dose is re-esterified to etretinate and so the risks of teratogenicity remain. In women of childbearing age, the possibility of pregnancy must be excluded before treatment and pregnancy must be avoided during treatment and for a

Panel 2: Outcomes used in clinical trials for psoriasis

Psoriasis area and severity index The psoriasis area and severity index (PASI) is a scoring procedure that is often used to evaluate psoriasis clinically and to measure outcomes in clinical trials. It scores the severity of lesions in terms of redness, thickness and scaliness, and the score is weighted according to the area affected.

In clinical trials, endpoints such as PASI 75 (a 75 per cent reduction in disease activity) and PASI 50 (a 50 per cent reduction in disease activity) are used. For patients with severe psoriasis, many clinicians consider at least a 75 per cent improvement to be clinically meaningful in terms of treatment success. Sometimes, patients perform the PASI assessment themselves and it is called a self-administered PASI (SAPASI).

Psoriasis disability index The psoriasis disability index (PDI) is a questionnaire usually completed by the patient, who must be over 16 years of age. It involves the patient answering a series of questions (by ticking boxes) about how psoriasis affects his or her daily activities, personal relationships and treatment. This gives an evaluation of the extent that psoriasis impairs the patient's quality of life.

period of two years afterwards. Because of the difficulty of meeting these provisions in practice, many dermatologists prefer not to recommend acitretin for women of childbearing age.

Acitretin is indicated for severe psoriasis and is often used in combination with PUVA (known as Re-PUVA — retinoid plus PUVA). The maximum effect is seen after four to six weeks. The most common side effects involve skin and mucous membranes, such as dry and cracking lips, dry skin and mucosal surfaces, hair thinning, paronychia, and soft and sticky palms and soles. Liver function and blood lipids should be monitored.

Patients receiving systemic treatment for psoriasis require careful monitoring and scrupulous attention to their other drug therapy to ensure that they are using the treatment appropriately and that they are not suffering from side effects or interactions.

Biological products

Some biological products (eg, monoclonal antibodies and fusion proteins) have been licensed for the management of psoriasis and many others are in development. All interfere with T-cell function at one stage or another. The modes of action can be broadly categorised into four groups:

- Inhibition of T-cell activation
- Inhibition of T-cell proliferation
- Induction of T-cell destruction
- Blocking effector cytokines

As yet, drugs in two of these groups have been granted licences, but so far, only one drug (efalizumab) in the UK. Alefacept (Amevive) has been licensed for the treatment of psoriasis in the US. Alefacept is a fusion protein that selectively binds to T-cells and prevents the second, co-stimulatory signal being sent, and thereby reduces the number of activated T-cells. It also mediates T-cell elimination by inducing apoptosis.

Infliximab and etanercept are licensed for the treatment of psoriatic arthritis. However,

infliximab, a monoclonal antibody directed against the effector cytokine TNF- α , and etanercept, which competitively binds TNF- α , have also been studied in psoriasis and appear to be effective for inducing remission.

There are still many hurdles to be overcome before treatment for psoriasis using biologics becomes the mainstream approach. The estimated annual cost of treatment is about £7,000. About a third of patients treated experience a rapid clinical improvement (with the exception of infliximab), whereas others respond rather slowly and moderately, and some do not respond at all. It will, therefore, be important to find ways to identify patients who can expect to benefit from these drugs. Although these drugs are described as "immunomodulatory" the risks of immunosuppression are not known and increased risks of infection and reactivation of tuberculosis or some lymphomas must be considered.

Looking at the evidence

With the range of therapies available and in development to treat psoriasis, pharmacists will need to be aware of the results of clinical trials and reviews in this area. Panel 2 describes two outcomes often used in clinical trials for psoriasis treatments.

The National Institute for Clinical Excellence is preparing a technology appraisal for efalizumab and etanercept, due to be published in February 2006.

Resources

- Reducing the harm caused by oral methotrexate. Patient Safety Alert 03. National Patient Safety Agency. July 2004. www.npsa.nhs.uk
- Immunomodulatory drugs for psoriasis. Boehncke W-H. *BMJ* 2003;327:634-5.
- Medonca CO, Burden AD. Current concepts in psoriasis and its treatment. *Pharmacology and Therapeutics* 2003;99:133-47.

Efalizumab is licensed for treatment of moderate to severe chronic plaque psoriasis in patients whose disease is unresponsive or who are intolerant to other therapies

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Visit www.npsa.nhs.uk and read the checklist for safe dispensing practice and recommended patient information leaflet for methotrexate. Apply these principles to your practice.
2. Look out for the NICE appraisal of efalizumab and etanercept for psoriasis in 2006.
3. Review the drugs that interact with ciclosporin.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

Correction

Etanercept is licensed for the treatment of adults with moderate to severe plaque psoriasis and not as stated. The recommended dose for this indication is 25mg twice weekly. The licence for this indication was granted in November 2004.