

Therapeutic management of psoriasis

By SAMUEL BUNDU-KAMARA, MSc, MRPharms

The second part of this month's special feature discusses the current management of psoriasis as well as new drugs being developed to treat the condition

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Applying dithranol in Lassar's (zinc and salicylic acid) paste to the back of a patient with severe psoriasis

Psoriasis is a psychologically and physically disabling, chronic, relapsing and inflammatory skin disease that affects 1–3 per cent of the world population.¹

The disease manifests itself as areas of thickened, scaly, silvery-white and reddened skin due to the distinct pathological changes that generally characterise this disorder. These are inflammation, hyperproliferation of the epidermis, altered maturation of the epidermis and vascular alterations which add to the redness.² Recent research has shown that these processes are mainly driven by activated T cells or antigen-presenting cells. These cells release various chemokines and cytokines to induce keratinocyte hyperproliferation, leading to abnormal differentiation.³

There are several different clinical subtypes of psoriasis: psoriasis vulgaris (chronic plaque), as well as the guttate, erythrodermic, pustular and palmoplantar forms of psoriasis. Patients may progress from one clinical subtype to another during the course of their lifetime.²

At present, psoriasis has no cure, but patients will experience periods of exacerbation and remission.

MANAGEMENT OPTIONS

Some patients with mild disease do not require any pharmacological intervention. Interventions with antipsoriatic treatments are normally started if the patient has problematic local symptoms such as itching, severe skin involvement or

Mr Bundu-Kamara is principal pharmacist with the St John's dermatology centre, which is based at St Thomas Hospital, London

psychological problems. The goal of treatment is to control the extent and severity of the disease so that it has minimal impact on the patient's quality of life.

In selecting a suitable agent, consideration should be given to the extent of the disease and the body areas involved. For chronic plaque psoriasis with involvement of less than 20 per cent of the body surface area, initial therapy is topical.

Systemic therapy or phototherapy is indicated when the disease affects more than 20 per cent of the body surface area or if the patient is unresponsive to topical therapy or psychologically disabled. The age and sex of the patient, as well as their general health, knowledge, previous treatment and preferences are also important.⁴

TOPICAL TREATMENT

Topical agents are used either alone or in combination with other topical agents or phototherapy. The topical agents used are emollients, keratolytics, coal tar, dithranol, topical vitamin D₃ analogues and topical retinoids.

Emollients There are few comparative trials that have examined the efficacy of different emollients used in psoriasis patients, but emollients have a role to play in patients with mild psoriasis. They hydrate and soften the scaly, hyperkeratotic surface of the plaques. Itchiness, soreness, redness, scaling and lesional extension have been reduced in 35 per cent of patients from twice daily application of emollients.¹ Emollients such as 50 per cent white soft paraffin with 50 per cent liquid paraffin, which have an ointment base, tend to be superior moisturisers because of their hydrating and occlusive effect.¹ However, they are

generally not accepted by patients because of their greasy feel and shiny appearance. Emollients should be applied to the skin as often as necessary in order to achieve good moisturising effect. Examples of moisturisers are Diprobase cream, E45 cream, and Epaderm.

Keratolytic agents Salicylic acid is the most widely used keratolytic agent in psoriasis. It softens the scaly layers of psoriatic plaques and eases their removal. It is applied to palms, soles and the scalp in concentrations of 2–10 per cent. Salicylic acid is used alone, as Lassar's (zinc and salicylic acid) paste or in combination with corticosteroids to enhance penetration of the latter and improve clinical efficacy.⁵ For example, salicylic acid is combined with 0.05 per cent betamethasone dipropionate in Diprosalic for the treatment of psoriasis at a maximum dose of 60g per week (Diprosalic scalp application contains 2 per cent salicylic acid, while Diprosalic ointment contains 3 per cent). Salicylic acid is an irritant and, when used extensively at high concentrations, can lead to salicylate toxicity.

Topical coal tar Coal tar is still used in many different formulations, ranging from ointments to shampoos, in the management of chronic psoriasis despite concerns about its safety.

Coal tar contains thousands of different chemical compounds and its precise mechanism of action is not known. Nevertheless, it does demonstrate antiproliferative and anti-inflammatory actions. There is published evidence of its efficacy in psoriasis. In one study comparing coal tar and emollients, a 48 per cent improvement was seen in the coal tar group compared with a 35 per cent

improvement in the emollient group.⁶ No difference in effectiveness was found between lower (5 per cent) and higher (25 per cent) concentrations of crude coal tar preparations.⁷

A synergistic effect is seen when coal tar is combined with other treatments, for example, with ultraviolet B (UVB) radiation, in the Goeckerman regimen, or with moderately potent steroids, such as 5 or 10 per cent coal tar solution in 0.025 per cent betamethasone valerate ointment.⁸ Coal tar preparations can be applied twice a day, that is, in the morning (showered off after 10–15 minutes) and at night (allowing the skin to dry for 10–15 minutes before the patient goes to bed).

The use of coal tar is limited by patient acceptability. In addition to its unpleasant odour, it can also stain clothing and bedding. The potential carcinogenic risk associated with coal tar, as identified in some studies, has led to a decline in its use. Studies have shown that the use of coal tar shampoos results in the absorption of appreciable amounts of polycyclic aromatic hydrocarbons, which have been identified as carcinogenic.⁹ This has led to some countries banning the use of coal tars in shampoos and the reduction of benzo-a-pyrene (a known carcinogen in coal tar) in coal tar products.⁸ At present, no epidemiological evidence exist of topical coal tar preparations causing cutaneous or internal cancer. Other side effects include folliculitis and contact allergy, and one reported case of severe bronchospasm in an atopic patient with asthma after inhalation of coal tar vapour.⁸

Topical dithranol Dithranol is oxidised to form highly reactive free radical compounds that are thought to inhibit deoxyribonucleic acid (DNA) synthesis. It is available in ointments, creams and pastes. Treatment usually starts with dithranol 0.1 per cent in "non-smudging" Lassar's paste. The strength of the preparation is then increased every four or five days, depending on the degree of irritation and clinical response. In the Ingram regimen, daily coal tar baths are followed by UVB phototherapy, and then by 24 hours application of dithranol paste. Patients with plaque psoriasis respond after approximately 20 days of treatment, and relapse at a rate of 10 per cent per month.¹⁰ It is also possible to apply higher concentrations of dithranol (1–8 per cent) for 15–30 minutes, using the "short contact" regimen, before washing it off. This allows sufficient dithranol to remain fixed to the plaque for a clinical effect and less risk of smudging dithranol on perilesional skin. The use of dithranol has declined steadily since the introduction of topical vitamin D₃ analogues, due to its unwanted

side effects of skin staining and irritation.

A new formulation of dithranol has led to better acceptance. The new product, Micanol, contains dithranol microencapsulated in a crystalline monoglycerine formulation that is temperature-sensitive and releases the dithranol at skin surface temperatures, producing less staining of the skin.¹¹ This formulation must be washed off with cold water because dithranol can be released from the temperature-sensitive vehicle by warm water.

Topical corticosteroids Topical corticosteroids are used extensively in the different clinical subtypes of psoriasis. They are effective, cosmetically acceptable and safe if used in the correct dose. Corticosteroids have anti-inflammatory, immunosuppressive and antiproliferative properties. They bind to a receptor in the cytoplasm of cells and are transported to the nucleus, where they affect gene transcription.¹² They remain the mainstay of psoriasis therapy in the United States,¹³ but are used in the UK mainly for resistant conditions and sites where other topical agents are poorly tolerated, such as the face, scalp and flexures. They are effective when applied once or twice a day, as monotherapy or in combination with tar and dithranol.¹

Topical corticosteroids range from mild preparations (1 per cent hydrocortisone) to highly potent ones (0.05 per cent clobetasol propionate). Lotions, solutions, creams, emollients, ointments, gels and sprays are available under several brand names. Corticosteroid-impregnated tapes, such as Haelan, are also available. These are useful for lichenified plaques that are refractory to other topical corticosteroids. Topical corticosteroids cause vasoconstriction, which correlates well with clinical efficacy and has been used to rank the potency of different preparations. Potency also depends on the excipients used in the formulation, for example, propylene glycol can enhance percutaneous absorption.

Corticosteroids have numerous side effects which have limited their use, for example, thinning of the skin, telangiectasia and steroids striae. One of the most problematic side effects is the development of tachyphylaxis with repeated use, which can transform stable psoriasis to unstable or pustular psoriasis.¹³ Recent developments in topical steroids have led to products such as mometasone furoate¹⁴ and fluticasone propionate,¹⁵ which are claimed to have fewer side effects in psoriasis patients despite their potencies.

Topical vitamin D₃ analogues The vitamin D₃ analogues are regarded by many as the first line treatment for patients with

mild to moderate chronic plaque psoriasis. There are few published data to support their use in other clinical subtypes of psoriasis. In the UK, two topical vitamin D₃ analogues are available: calcipotriol and tacalcitol. They act by inhibiting epidermal cell proliferation and by enhancing cell differentiation. Calcipotriol is licensed for once or twice daily application and available in ointment and cream formulations containing calcipotriol at a concentration of 50µg/g and as a scalp lotion (50µg/ml). The maximum dose should not exceed 100g weekly for creams and ointments or 60ml weekly for scalp lotions, otherwise there is an increased risk of hypercalcaemia. Tacalcitol is licensed for once-daily application and available as an ointment containing 1,24-dihydroxycholecalciferol at a concentration of 4µg/g. The rate of application should not exceed 10g of ointment per day.

Calcipotriol has been shown in studies to have higher efficacy than placebo and other topical treatments. When compared with topical corticosteroids, calcipotriol was significantly more effective at six weeks but not at eight weeks.¹⁶ It is also more effective than coal tar and short contact therapy and its efficacy is enhanced when combined with UVB phototherapy.¹⁶ The combination of a potent corticosteroid with calcipotriol was more effective than calcipotriol alone and also avoided some of the irritation of calcipotriol.¹⁷ An ointment containing calcipotriol and 0.5mg/g betamethasone was launched recently. Calcipotriol, applied twice daily, was more effective than once-daily tacalcitol treatment at eight weeks.¹⁸

Topical calcitriol (1,25-dihydroxycholecalciferol), when applied to psoriasis plaque as a 3µg/g calcitriol ointment is an effective and safe treatment. Three double blind, vehicle-controlled trials showed that calcitriol has good clinical efficacy. In a left-right comparison of 3µg/g calcitriol ointment with ointment containing only the vehicle, complete clearance of psoriatic lesions was achieved in 48 per cent of calcitriol-treated sites, compared with 7 per cent of vehicle-treated sites. A further 41 per cent of the calcitriol-treated sites and 62 per cent of the vehicle-treated sites showed considerable or definite improvement. The clinical response to calcitriol in another study was as good as, or even better than, that achieved with 0.1 per cent betamethasone valerate ointment.¹⁹ Topical calcitriol is not yet available in the UK.

Topical vitamin D₃ analogues are more aesthetically acceptable to patients than some of the older topical treatments such as coal tar and dithranol. However, lesional and perilesional irritation are reported to be common side effects, and for this reason, they are generally not used on

facial lesions and flexures.

Maxacalcitol, a new vitamin D₃ analogue currently under development, is as effective as calcipotriol, based on primary efficacy parameters (psoriasis severity index — based on erythema, scaling, induration and investigators' overall assessments of patients) but more effective than placebo and calcipotriol at 25µg/g than placebo and calcipotriol, based on secondary parameters (investigators' and patient preference).²⁰

Retinoids Tazarotene is currently the only topical retinoid licensed for the treatment of mild to moderate plaque psoriasis on the trunk and limbs covering up to 10 per cent of the body surface area. Tazarotene reduces the abnormally high rate of epidermal keratinocyte proliferation and the lack of differentiation of epidermal cells that characterise psoriasis, possibly by inducing expression of three tazarotene-induced genes (TIG-1, TIG-2 and TIG-3) in the human epidermis.¹⁸ It is available as gels containing 0.05 per cent and 0.1 per cent of tazarotene, and is applied once daily for up to 12 weeks. Like calcipotriol, it avoids the side effects of corticosteroids. The main side effect is irritation at the site of application, especially when the 0.1 per cent formulation is used as monotherapy. Tazarotene should not be applied to the face, intertriginous areas or scalp. There is a small risk of systemic absorption following topical application, therefore it should not be used in women of childbearing age, due to the teratogenicity of retinoids.²¹

The efficacy of tazarotene has been demonstrated in various clinical trials. When patients with mild to moderate psoriasis were treated with tazarotene 0.05 per cent or 0.1 per cent gel once daily for 12 weeks, 60 to 70 per cent of patients achieved good, excellent or complete clearance compared with 35 per cent of placebo-treated patients.²² When the 0.05 per cent or 0.1 per cent gel were compared with the topical corticosteroid fluocinonide cream (0.05 per cent twice daily) over 12 weeks, similar efficacy was seen in reducing plaque elevation and a durable response was seen after treatment discontinuation.²² Combining tazarotene 0.1 per cent gel with fluocinolone 0.05 per cent or mometasone furoate 0.1 per cent cream has been studied for the purpose of avoiding retinoid dermatitis. Higher efficacy against scaling and erythema was observed, compared with tazarotene alone.²³

The combination of UVB and tazarotene has also been studied. Patients were treated with tazarotene 0.1 per cent gel daily for two weeks, followed by tazarotene plus UVB therapy three times a week for 10 weeks. The patients treated with UVB and tazarotene responded more favourably

than patients treated with UVB alone.¹³

PHOTOTHERAPY

Ultra violet B radiation is used to treat patients who are refractory to topical treatment or who have widespread disease such as severe guttate and chronic plaque psoriasis. The UVB fluorescent source (wavelength 290–320nm) commonly referred to as broadband (TL12 UV6 lamps) has been superseded by a narrow band (TL-01) phototherapy source, because the latter produces greater improvement in terms of plaque clearance and length of remission.⁸ The dose of UVB used for treatment is based either on minimal erythema dose or on Fitzpatrick skin types (Panel 1).¹³ Treatment is usually carried out two or three times a week.

UVB is administered in combination with a variety of topical or systemic therapy to achieve faster results and higher effectiveness. An increased rate of clearance with reduced total UVB exposure can be seen when used in combination with tars, topical corticosteroids and oral retinoids.⁸ However, such combinations might actually increase the risk of photosensitivity reactions and burning.

Unwanted side effects from UVB phototherapy are skin burning, which can be avoided by careful dosimetry, and premature skin ageing from long-term use.

UVB is contraindicated in patients with malignancy and systemic lupus erythematosus. UVB can be used in children and pregnant women and does not require any ultraviolet A (UVA) eye protection after treatment (see psoralens and ultraviolet A [PUVA] below).

Photochemotherapy Photochemotherapy involves the administration of oral or topical psoralens followed by irradiation with long wave UVA (320–400nm). 8-Methoxypsoralen (8-MOP) at a dose of 0.6mg per kg is the drug most commonly given two hours before UVA light treatment (see Table 1, p195). Once peak levels are attained, irradiation results in the formation of pyrimidine dimers and cross-linkage of DNA strands. This disrupts DNA synthesis, thereby inhibiting cell proliferation. Treatment is administered two or three times a week, and improve-

Panel 1: Fitzpatrick skin types

- 1 Always burns, never tans
- 2 Always burns, sometimes tans
- 3 Always tans, sometimes burns
- 4 Always tans, never burns
- 5 Asian
- 6 Black

Panel 2: Recommendations for using methotrexate

Baseline monitoring

History and physical examination
Complete blood cell and platelet counts
Liver function tests, blood urea, nitrogen level, creatinine level
HIV testing, if at risk

Follow-up monitoring

Complete blood cell and platelet counts weekly, then every four weeks
Liver function tests, blood urea nitrogen level, creatinine level every four to eight weeks
Repeat blood counts seven days after dose escalation

Dosage

Test dose: 2.5–5mg
Average dose: 10–15mg per week
Maximum dose: 30mg per week
When improved, taper by 2.5mg per month

ment or clearance is seen in 90 per cent of patients after 20–30 treatments.¹³

Two main PUVA regimens are used. One involves using the minimal phototoxic dose (MPD) and increasing the dose in increments depending on the presence or absence of erythema. The other approach is to use a fixed starting dose, which will vary with skin type, followed by fixed or percentage increments.

PUVA therapy has some adverse effects, most commonly nausea, skin burning and pain. Chronic adverse effects are skin ageing, pigmentation and carcinogenicity. Nausea can be avoided by administering the dose of psoralen over 15 minutes and ingesting it with food. Another strategy for preventing nausea involves ingesting ginger 20 minutes before psoralen. If nausea occurs with 8-MOP, then either 5-MOP or bath PUVA using 8-MOP or trimethoxypsoralen (TMP) can be considered. (In bath PUVA, the patient lies in a bathtub of water in which psoralen has been dissolved. Afterwards, the patient is exposed to UVA radiation.) There is also the theoretical risk of cataract formation, therefore patients are advised to wear UVA eye protection for up to 24 hours. The risk of cutaneous malignancy and particularly squamous cell carcinomas increases in patients if more than 150 treatment sessions are given. In one study, an 11-fold increase in squamous cell carcinomas was observed in patients treated with 260 sessions compared with patients who had received fewer than 160 sessions.²⁴ In men, there is a higher incidence of genital skin cancer, therefore the genitals should be shielded

during treatment.²⁵ An increased risk of melanoma is observed in PUVA-treated patients exposed to high doses, and the risk appears to increase with the passage of time.²⁶

PUVA is administered in combination with other drugs to reduce some of its side effects or to minimise the total cumulative dose of PUVA or other forms of treatment. PUVA has been combined with topical corticosteroids, vitamin D₃ analogues, and tazarotene, with varying outcomes. When combined with oral retinoids (Re-PUVA), a synergistic effect was seen, along with a mutual reduction of their side effects. The number of treatments required for clearing the disease was also reduced, and the retinoid had a PUVA-sparing effect. The combination of PUVA with oral retinoids results in a much more effective treatment of psoriasis than retinoids monotherapy.²⁷ Also, combination of PUVA and UVB therapy has been tried and in one study, a mean of only 11.3 treatments and much lower doses of UVB and UVA than with monotherapy were required for clearance.²⁸

SYSTEMIC THERAPY

Systemic therapies are used by dermatologists in the hospital setting for patients with unresponsive severe disease. The patient should understand the need for the drugs and their side effects. The systemic agents used in psoriasis should be tailored for each patient, because they are accompanied by potentially serious side effects, different toxicity profiles and contraindications. Patients with recalcitrant or severe psoriasis are sometimes treated with combinations of systemic agents, and careful monitoring is needed.

Methotrexate, ciclosporin and acitretin are currently licensed in the UK for use in psoriasis, but some unlicensed drugs are also available.

Table 1 (p195) provides details of some agents used in the treatment of moderate to severe psoriasis.

Methotrexate Methotrexate (MTX) has been shown to be an effective treatment for psoriasis.⁸ It is indicated for severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of treatment. It is particularly beneficial for patients with psoriatic arthritis. MTX is a folate acid antagonist that reversibly inhibits dihydrofolate reductase, an enzyme that converts folic acid to tetrahydrofolic acid. MTX therefore blocks an essential step in DNA synthesis. MTX is given orally, intramuscularly or intravenously as a single dose once a week. A test dose of 2.5–5mg is given to detect patients who may be sensitive to the drug.

If it is tolerated after seven days, the dose is gradually increased weekly to a maintenance dose of 10–25mg per week.

MTX is excreted renally so patients with significant renal impairment should not be prescribed MTX. Other side effects include teratogenicity, haematological abnormalities, nausea, leucopenia and thrombocytopenia. It is also an abortifacient. Bone marrow toxicity is the most serious short-term side effect but hepatotoxicity is the most common long-term effect. Therefore, patients are advised to avoid alcohol intake while on MTX.

Guidelines for the use of MTX in psoriasis have been developed²⁹ in order to avoid these side effects (see Panel 2). The most controversial aspect of the guidelines has been the recommendation for liver biopsy. Initially, liver biopsy was advocated before the initiation of MTX therapy, but the recent guidelines state that patients with normal liver function tests and without a history of liver disease or alcoholism should not undergo biopsy until they have taken a cumulative dose of 1–1.5g. Repeat biopsies are done every 1–1.5g thereafter if liver function tests and biopsy are normal. In patients with a history of liver disease, the first liver biopsy is performed after two to four months of therapy.²⁹ An alternative to biopsy is performing an assay of amino propeptide of type III procollagen (PIIINP) every three months and liver biopsy only for patients with persistently abnormal results.³⁰ A normal PIIINP indicates absence of fibrosis, but it is not as specific as biopsy.

Folic acid supplementation (5mg daily) is used to counteract the nausea caused by MTX therapy. A recent study of 22 patients with stable psoriasis controlled with MTX and who were given folic acid 5mg supplementation or placebo for 12 weeks, showed a worsening of psoriasis area and severity index (PASI) and quality of life measures compared with the placebo group.³¹ This study suggests that folic acid supplementation does reduce the efficacy of MTX therapy and therefore should only be given to patients experiencing MTX-induced nausea and not as a routine measure.

MTX also interacts with many other drugs, and this should be borne in mind before it is prescribed. The nature of the interaction is either drug displacement or competition for renal tubular secretion or both. MTX interacts with ciclosporin to produce an additive immunosuppression, and interaction with retinoids will increase the risk of hepatotoxicity. MTX also interacts with non-steroidal anti-inflammatory drugs (NSAIDs), penicillins, acitretin, cotrimoxazole, probenecid and trimethoprim as recorded in the standard sources of information on drug interactions.

Table 1: Photochemotherapeutic and systemic agents used in the treatment of moderate to severe psoriasis^{8,39}

Class	Photochemotherapy Psoralen + UVA	Methotrexate Immunosuppressant	Ciclosporin Immunosuppressant	Acitretin Retinoid
Dosage	Oral 8-MOP: 0.6mg per kg two hours before UVA. Oral 5-MOP: 1.2mg per kg three hours before UVA	10–25mg once weekly	Initially, 2.5mg per kg daily in two divided doses, increased gradually to a maximum of 5mg per kg daily if no improvement is seen within one month. Initial dose of 5mg per kg daily justified if condition requires rapid improvement	25–30mg daily for two to four weeks, then 25–75mg daily
Approximate response time	Four weeks	Six weeks	Six weeks	Six weeks
Side effects	Nausea, pruritus, erythema, PUVA lentiginos (dark spots that appear in patients undergoing PUVA therapy for prolonged periods), premature ageing of the skin, irregular pigmentation, cataract formation	Myelosuppression, liver cirrhosis, gastrointestinal symptoms, alopecia	Nephrotoxicity, hypertension, gastrointestinal symptoms, hypertrichosis, fatigue, neurological symptoms	Teratogenicity, hepatotoxicity, hyperlipidaemia, pancreatitis, potential skeletal effects, dry and cracked lips, alopecia, skin peeling, nail disorder, and arthralgia
Contraindications	Pregnancy and lactation, cataracts, age under 18, previous cutaneous malignancy, concomitant ciclosporin or methotrexate therapy, exposure to arsenic or ionising radiation, porphyria, photosensitivity disorders, cumulative lifetime dose greater than 1,500 joules per cm ² , hepatic impairment	Pregnancy, lactation, hepatitis (active or recent), cirrhosis, anaemia, leucopenia, thrombocytopenia, active infectious disease, diabetes or extreme obesity, alcohol consumption, renal impairment (reduce dose), immunodeficiency	Pregnancy and lactation, renal impairment, uncontrolled hypertension (diastolic blood pressure above 95mmHg), previous or concomitant malignancy, concomitant radiation treatment, immunodeficiency or immunosuppression, and drug or alcohol abuse	Pregnancy and lactation (or planning to conceive within two years of stopping treatment), severe hypercholesterolaemia or hypertriglyceridaemia, severe hepatic or renal impairment, concomitant methotrexate therapy
Precautions and monitoring	Contraception, UVA eye protection, shielding of genitalia unless specific need to treat, regular skin examination for premalignant and malignant changes	Contraception, avoid interacting drugs, full blood count, liver function test, serum urea and electrolytes, serum creatinine, PIIINP, consider liver biopsy	Contraception, blood pressure, serum creatinine	Contraception, liver function test and fasting serum lipids, annual lateral x-ray of thoracic spine

Ciclosporin is an immunosuppressant drug developed for the prevention of organ rejection after transplant. It is highly effective against all clinical subtypes and manifestations of psoriasis,¹² and is licensed in patients with extensive psoriasis where conventional therapy is either ineffective or inappropriate. Ciclosporin acts by blocking a calcineurin-dependent factor, which is essential for the production of interleukin-2 (IL-2) and hence the proliferation of activated T cells and other T cell cytokines.

Ciclosporin is prescribed as a short

course therapy for four to 12 weeks, but can be used as maintenance therapy or long-term continuous therapy. The dose range is 2.5–5mg per kg. Higher doses produce a more rapid response but 5mg per kg should not be exceeded, especially for long-term use, otherwise the patient will be more prone to side effects. The efficacy of ciclosporin has been confirmed in several double-blind placebo-controlled trials,^{32–34} and open trials.^{35,36} Ciclosporin (5mg per kg) has been compared with dithranol (2–8 per cent in emulsifying ointment plus UVB phototherapy) in the treatment of chronic plaque psoriasis.

Clearance was achieved at six weeks in the ciclosporin group but at eight weeks in the dithranol group.³⁷ The relapse rate was slightly higher in the ciclosporin group.

Regular monitoring is necessary for patients on ciclosporin, because the most frequent side effect is dose-dependent renal impairment. Patients should be reviewed fortnightly for eight weeks, and monthly or fortnightly if the dose has been changed or if there is any other cause for concern. Hypertension is common among patients taking ciclosporin and can be treated by dose reduction or by using a conventional antihypertensive.

Drug interactions are significant with ciclosporin because of its narrow therapeutic index. Interactions occur by inhibiting or inducing cytochrome P450 3A, which can reduce the efficacy or increase the toxicity of ciclosporin. Important examples of drugs inhibiting ciclosporin metabolism include diltiazem, erythromycin, itraconazole and verapamil. Drugs that can induce rapid ciclosporin metabolism include carbamazepine, phenytoin and rifampicin. Grapefruit juice can also increase ciclosporin plasma levels.

Oral retinoids Acitretin is the oral retinoid of choice for psoriasis. It is the active metabolite of etretinate, the first oral retinoid drug to be used for psoriasis. Etretinate has now been discontinued because it accumulates in body tissue and is teratogenic. Acitretin, a synthetic aromatic derivative of retinoic acid, has an inhibitory effect on psoriasis and disorders of epithelial keratinisation. It is capable of reversing hyperkeratotic and metaplastic skin changes. Acitretin is effective in the treatment of pustular (palmoplantar and generalised) and erythrodermic types of psoriasis. Studies have shown it to be effective as monotherapy, achieving 70 per cent clearance in approximately eight weeks.⁸ In a 20-week non-comparative study using a dose of 75mg per day, acitretin was shown to be effective in psoriatic patients with HIV infection, without exacerbating immunosuppression.³⁸ Good to excellent results were seen in six out of 11 patients. When combined with PUVA phototherapy, a rapid response rate and more extensive clearance of lesions compared with either treatment alone was seen.³⁹ One advantage of this combination is a reduction in the required dose for each treatment.

Acitretin is associated with a large number of side effects and toxicity reactions. Mucocutaneous reactions are the most common. These include dryness and cracking of lips in most patients, as well as skin peeling. Acitretin is teratogenic, and pregnancy should be avoided for at least two years after stopping therapy. Other side effects are elevation of serum lipids, particularly triglycerides, elevated liver enzymes, alopecia, and skeletal changes with long-term use, eg, calcification of ligaments and skeletal hyperostoses.

OTHER SYSTEMIC THERAPY

The following drugs, although not licensed for the treatment of psoriasis, will be covered briefly because they are reserved for patients who fail to respond to the treatment options discussed above or patients in whom standard treatments are contraindicated. They are sometimes used

in combination with the standard treatments in order to improve or speed up outcomes.

Hydroxycarbamide Hydroxycarbamide (hydroxyurea) is an antimetabolite that is used as a second or third line systemic agent for psoriasis. The recommended dose in adults is 1g initially, and this can be titrated according to efficacy and toxicity up to a maximum of 2g. There is only one controlled trial that demonstrates its effectiveness in psoriasis.⁹ The main side effect is myelosuppression, which manifests as megaloblastic anaemia. Other side effects include hyperpigmentation, fever, alopecia and elevation of liver enzymes. Hydroxy-carbamide should be avoided in women who are of child-bearing age due to the risk of teratogenicity.

Mycophenolate mofetil Mycophenolate is a novel immunosuppressive drug that is used for the prevention of organ transplant rejection. It has proven effective in the treatment of several inflammatory or autoimmune skin disorders such as bullous pemphigoid, pemphigus vulgaris and atopic dermatitis. It is used as an unlicensed medicine in psoriasis in doses up to 4g per day, although 2g per day is effective and safe in severe psoriasis.⁴⁰ Mycophenolate mofetil can be used in combination with ciclosporin and is used to taper the dose of ciclosporin in patients. Baseline monitoring for patients before starting treatment is required. Side effects include gastrointestinal and haematological toxicity.

Tioguanine Tioguanine is a purine analogue that is used in the treatment of leukaemia. Tioguanine is reserved as third line agent for patients with recalcitrant psoriasis because it can cause severe bone marrow suppression. Therefore, baseline and follow-up monitoring are essential when it is used in patients. The dose normally used is 80mg twice a week, increasing by 20mg every two to four weeks, up to a maximum of 160mg three times a week.⁴¹ Eleven out of 14 patients achieved improvement, with 10 of them experiencing 75 per cent clearance or greater. Other side effects include nausea, vomiting and elevation of liver enzymes.

Fumaric acid esters Fumaric acid esters, although not licensed in the UK, have been used in Germany and the Netherlands for several years for the treatment of psoriasis. They appear to work by causing a selective increase in TH2 cytokines. This is in effect an indirect cytokine switch, with a subsequent decrease in TH1 cytokines. After four months of treatment, an 80 per cent decrease in the psoriasis area and severity index (PASI) was seen in one

study.⁴² Discontinuation of treatment is common due to abdominal pain, diarrhoea and flushing. Lymphocytopenia and eosinophilia are also common. Therefore, the dose is gradually increased on a weekly basis from 30mg daily to 120mg three times a day.

Systemic corticosteroids Oral steroids are rarely used for the treatment of psoriasis because of their adverse effects and the risk of rebound flaring on discontinuation of treatment. They are only used in persistent or uncontrollable forms of the disease, such as erythrodermic or pustular psoriasis.

TREATMENT TECHNIQUES

Combinational, rotational and sequential techniques are used in the treatment of psoriasis.

In managing psoriasis, it is common to combine systemic therapies, phototherapy and topical agents in patients to achieve greater efficacy and reduce side effects. Also, lower doses of the individual agents are possible. The treatment combinations that have been used include:

- | Methotrexate + ciclosporin
- | PUVA + UVB
- | Retinoid + PUVA
- | Retinoid + UVB

Single agents can be rotated so that total cumulative doses are reduced. For example, a patient can be rotated through UVB plus coal tar, PUVA, methotrexate and retinoids.

Sometimes a sequential technique is employed. This involves rapid clearance by means of a potent medicine such as ciclosporin, followed by a transitional or maintenance phase with acitretin in combination with UVB or PUVA.

NEW DEVELOPMENTS

The exact aetiology of psoriasis is still unknown but research over the past 10 years has given us an insight into the roles of genetics and immunology in the disease pathogenesis. The effectiveness of ciclosporin in psoriasis has shown that the disease is mediated by T cells. This has led to the strategic development of new drugs. **Targeting T cells** Targeting leucocyte function associated antigens (LFA) adhesion molecule ligands, which play an important role in T cell activation is one method under investigation. They are essential for cutaneous lymphocyte migration, adhesion and activation. An immunoglobulin G, IgG-LFA-3 fusion protein, alefacept, which blocks T cell binding (via CD2 receptor) to LFA-3 on antigen-presenting cells has recently been approved in the US

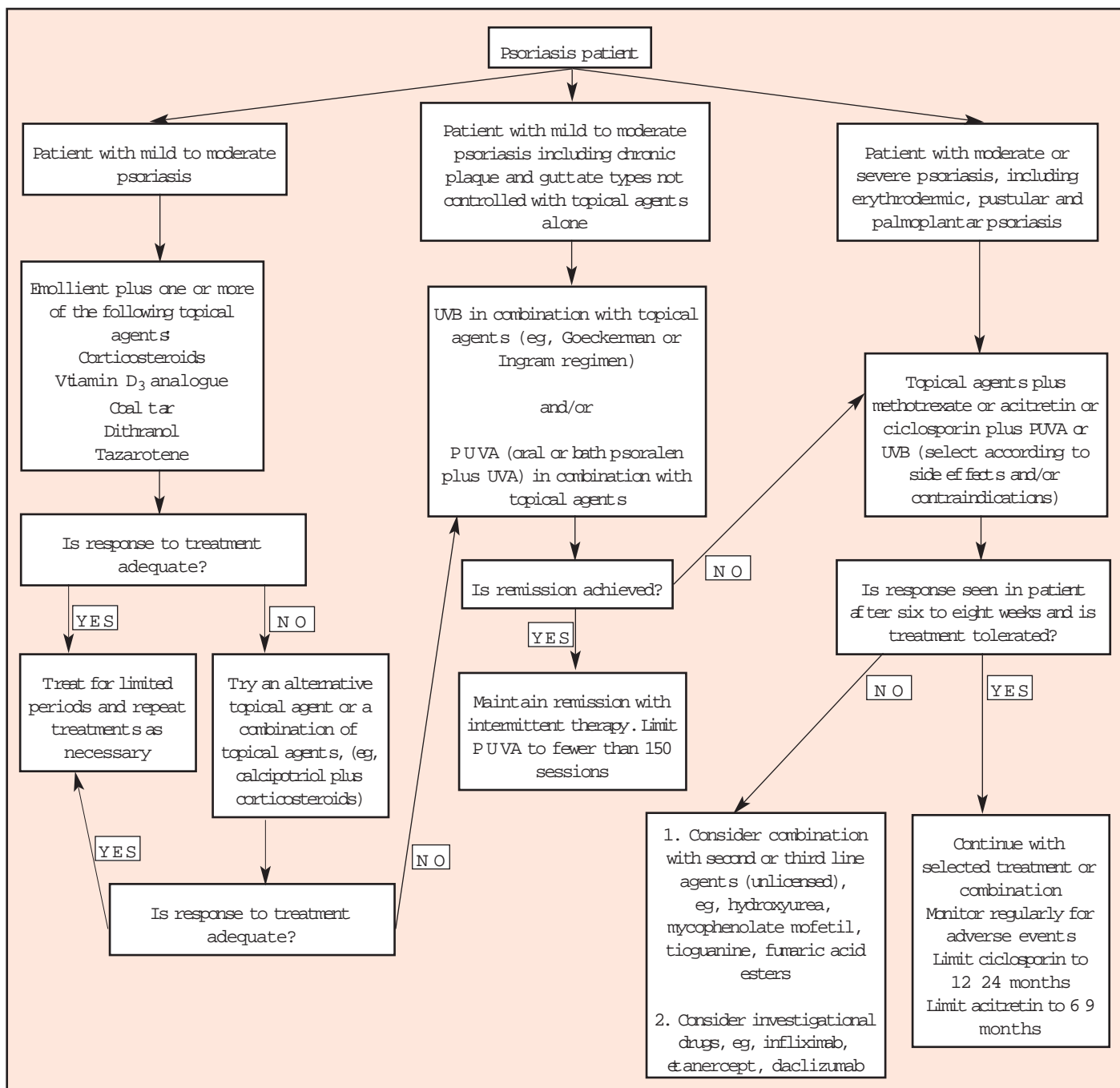


Figure 1: Management options for psoriasis patients³⁹

for use in moderate to severe chronic plaque psoriasis. In a randomised, placebo-controlled trial involving 229 patients with moderate to severe psoriasis, intravenous alefacept (0.025, 0.075 or 0.150mg per kg) or placebo was administered once a week for 12 weeks. Alefacept caused a mean reduction in PASI of 38 per cent, 53 per cent and 53 per cent respectively when compared with placebo (21 per cent) after two weeks.⁴³ Alefacept can be given by intravenous or intramuscular administration and the T cell count of patients should be monitored frequently.

Daclizumab is an immunosuppressive humanised monoclonal antibody that targets the alpha chain of the interleukin-2 (IL-2) receptor (CD25) expressed on

activated T cells. Binding of daclizumab to the receptor results in the inhibition of the proliferative signal from IL-2, a decrease in the production of IL-2, and a decrease in T cell proliferation in response to IL-2. Daclizumab produced a 30 per cent improvement in psoriasis over 16 weeks.⁴⁴

Furthermore, an antibody to CD11a, a subunit of LFA-1 and a cytotoxic T lymphocyte, CTLA4IgG fusion protein, that blocks CD28, all look like promising candidates.⁴⁵ Interference with activated T cells in these ways is expected to produce specific immunomodulation, which is less toxic.

Modulation of cytokines Psoriasis lesions have a distinctive cytokine pattern. They

are predominantly cytokine TH1 subtypes characterised by high levels of interferon gamma and tumour necrosis factor (TNF) alpha. Switching or modulating the T cell response to TH2 cytokines, that is, IL-4 and IL-10, has been shown to benefit patients.

Infliximab, a monoclonal chimeric anti-TNF-alpha antibody currently licensed for rheumatoid arthritis and Crohn's disease, has been shown in a randomised, placebo-controlled trial to be highly effective in severe plaque psoriasis. Nine out of 11 patients responded to infliximab 5mg per kg anti-TNF-alpha and 10 out of 11 patients responded to the 10mg per kg dose.⁴⁶ At St John's dermatology centre, infliximab has been used in two patients with recalcitrant psoriasis. The initial response was good but tolerance was

encountered with subsequent doses. Similarly, etanercept, a recombinant TNF receptor (TNF-R2) fusion protein, has been reported to be an effective and well-tolerated therapy in psoriatic arthritis and psoriasis.⁴⁷

IL-10, an anti-inflammatory cytokine, has also been tested in psoriasis patients, with moderate effects.⁴⁸

Mycobacterium vaccae vaccine can also cause TH2 cytokine switch and improve psoriasis when injected intradermally.⁴⁹

Topical immunosuppressive agents Research into less toxic systemic and topical immunomodulatory drugs has led to the development of topical ascomycin (SDZ ASM 981), a macrolide antibiotic, which is effective in atopic dermatitis. Initial results show that ascomycin is only effective when occluded. An oral formulation of the drug is currently being investigated.⁵⁰ Another topical macrolide, tacrolimus, is also only effective in clearing psoriasis when occluded.⁵¹

Nuclear receptor therapies Liarazole, a new class of retinoid-mimetics, known as retinoic acid metabolism blocking agents (RAMBAs) has been found to be efficacious in chronic plaque and palmoplantar pustular psoriasis in a dose ranging study, with similar efficacy to acitretin⁵² but without the latter's side effects profile. Liarazole is not a retinoid; it acts by increasing tissue and plasma content of endogenous retinoids which returns to normal within one to two days of stopping the drug. The peroxisome proliferator-activated receptor (PPAR) is a more recently identified member of the thyroid/steroid nuclear receptor family. Blockage of PPAR receptor by thiazolidinediones (eg, troglitazone, an oral hypoglycaemic agent for the treatment of type II diabetes) has been shown to be efficacious in chronic plaque psoriasis.⁵³ However, troglitazone has been withdrawn recently due to hepatotoxicity.

Other recent developments include the greater awareness of the role of psychological intervention in psoriasis patients, and studies have been carried out on the use of adjunctive psychological interventions in patients who receive conventional therapy in order to improve clearance.⁵⁴ There has also been the development of photodynamic therapy, the concomitant use of porphyrin analogues and the use of laser or non-laser visible light. Photodynamic therapy has the advantage of tissue-selectivity and is non-damaging to normal skin. It is showing great potential in psoriasis treatment.⁵⁵

CONCLUSION

Great advances have been made in the understanding of the pathogenesis of psoriasis and this has led to the use of new therapies for patients. The aim of these developments, as in other areas of medicine, is to reduce toxicity and side effects and increase patient compliance. Topical therapies still have a vital role to play in the management of psoriasis but the use of dithranol and coal tar will continue to decline as new vitamin D₃ analogues and topical retinoids enter the market. The latter class of drugs possess better efficacy and a better patient acceptability profile.

Combination therapies of topical agents, systemic agents and/or phototherapy, are the treatments of choice for most patients because of the synergistic effects and the reduction in dose and side effects they offer (see Figure 1 for management algorithm).

Future management strategies will involve the greater recognition and understanding of psychological distress as a trigger of the disease process and it is to be hoped that as our genetic knowledge of the disease improves, gene therapy could become an option. The development of an animal model for psoriasis may also be achieved. Such a model would allow rapid screening of potential therapies, and a possible role for pharmacogenetics, that is, individually selecting a drug treatment for the greatest efficacy and the least side effects.

Credit for Learning begins on p211

REFERENCES

1. Greaves MW, Weinstein GD. Treatment of psoriasis. *N Engl J Med* 1995;332:581-8.
2. Stern SR. Psoriasis. *Lancet* 1997;350:349-53.
3. Nickoloff BJ. The immunologic and genetic basis of psoriasis. *Arch Dermatol* 1999;135:1104-10.
4. Tan S, Tremaine R, Reardon M. Overview of the pathogenesis and treatment of psoriasis. *Drugs Ther* 1996;19:1-6.
5. Federman D, Froelich C. Topical psoriasis therapy. *American Family Physician* 1999;59:957-62.
6. Kanzler MH, Gorsulowsky DC. Efficacy of topical 5 per cent liquor carbonis detergens versus its emollient base in the treatment of psoriasis. *Br J Dermatol* 1993; 129:310-13.
7. Williams REA, Tillman D, White SI, Barnett EL, Mackie RM. Re-examining crude coal tar treatment for psoriasis. *Br J Dermatol* 1992;126:608-10.
8. Gawkrödger DJ. On behalf of the therapy guidelines and audit subcommittee of the British Association of Dermatologists. Current management of psoriasis. *J Dermatol Treatment* 1997;8:27-55.
9. Schooten FJ, van Moonen EJC, Rhijsburger E, Agen BV, Thijssen HW, Kleinjans JCS. Dermal uptake of polycyclic aromatic hydrocarbons after hairwash with coal-tar shampoo. *Lancet*

- 1995; 344:1505-6.
10. Vella Briffa D, Greaves MW, Warin AP, Rogers S, Marks J, Shuster S. Relapse rate and long term management of plaque psoriasis after treatment with photochemotherapy and dithranol. *BMJ* 1981;282:937-40.
11. Volden G, Bjornberg A, Tergner E et al. Short-contact treatment at home with Micanol. *Acta Derm Venereol Suppl (Stockh)* 1992;172:20-2.
12. Ashcroft A, Li Wan Po A, Griffiths CEM. Therapeutic strategies for psoriasis. *J Clin Pharm Ther* 2000;25:1-10.
13. Lebwahl M, Ali S. Treatment of psoriasis. Part 1. Topical therapy and phototherapy. *J Am Acad Dermatol* 2001;45:487-98.
14. Tan MH, Meador SL, Lebwahl MG. The safety and efficacy of limited application of fluticasone propionate ointment 0.005 per cent in patients with psoriasis of the face and intertriginous areas. Poster Abstract Book of the 57th annual meeting of the American Academy of Dermatology; 1999 Mar 19-24; New Orleans. New Orleans: American Academy of Dermatology; 1999, abstract 463.
15. Lebwahl M, Peets E, Chen V. Limited application of mometasone furoate on the face and intertriginous areas: analysis of safety and efficacy. *Int J Dermatol* 1993;32:830-1.
16. Ashcroft DM, Li Wan Po A, Williams HC, Griffiths CME. What is the role of topical calcipotriol in the treatment of mild to moderate chronic plaque psoriasis? *BMJ* 2000;320:963-7.
17. Kragballe K, Barnes L, Hamberg K, Hutchinson P, Murphy F, Moller S. Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: tolerability and efficacy. *Br J Dermatol* 1998;139:649-64.
18. Veien NK, Bjerke JR, Rossmann-Ringdahl I, Jakobsen HB. Once daily treatment of psoriasis with tacalcitol compared with twice daily treatment with calcipotriol: a double-blind trial. *Br J Dermatol* 1997;137:581-6.
19. Langner A, Stapor W, Ambroziak M. Efficacy and tolerance of topical calcitriol 3 µg/g in psoriasis treatment: a review of our experience in Poland. *Br J Dermatol* 2001;144(suppl 58):11-16.
20. Barker JNWN, Ashton RE, Marks R, Harris RI, Berth-Jones J. Topical maxacalcitol for the treatment of psoriasis vulgaris: a placebo-controlled, double-blind, dose finding study with active comparator. *Br J Dermatol* 1999;141:274-8.
21. Tazarotene — a topical retinoid for psoriasis. *Drug Ther Bull* 1999;37:47-8.
22. Weinstein GD. Tazarotene gel: efficacy and safety in plaque psoriasis. *J Am Acad Dermatol* 1997;37(2part3):S33-8.
23. Lebwahl M, Breneman DL, Goffe BS, Grossman JR, Ling MR, Milbauer J et al. Tazarotene 0.1 per cent gel plus corticosteroids cream in the treatment of plaque psoriasis. *J Am Acad Dermatol* 1998;39:590-6.
24. Stern RS, Lange R. Non-melanoma skin cancer occurring in patients treated with PUVA five to 10 years after first treatment. *J Invest Dermatol* 1988;91:120-4.
25. Stern RS. Genital tumors among men with

- psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. The photochemotherapy follow-up study. *N Engl J Med* 1990;322:1093-7.
26. Stern RS. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001;44:755-61.
 27. Lebwohl M. Acitretin in combination with UVB or PUVA. *J Am Acad Dermatol* 1999;41(suppl):S22-4.
 28. Momtaz TK, Parrish JA. Combination of psoralens and ultraviolet A and ultraviolet B in the treatment of psoriasis vulgaris; a bilateral comparison study. *J Am Acad Dermatol* 1984;10:481-6.
 29. Lebwohl M, Ali S. Treatment of psoriasis. Part 2. Systemic therapies. *J Am Acad Dermatol* 2001;45:649-61.
 30. Zachariae H, Heichendorff L, Sogaard H. The value of amino-terminal propeptide of type III procollagen in routine screening for methotrexate-induced liver fibrosis: a 10-year follow up. *Br J Dermatol* 2001;143:100-03.
 31. Tan E. The use of folic acid supplementation in methotrexate-treated psoriatics. Program and abstracts of the 60th annual meeting of the American Academy of Dermatology; 2002 Feb 22-27; New Orleans. New Orleans: American Academy of Dermatology; 2002, p148 [exhibit 22].
 32. Ellis CN, Gorsulowsky DC, Hamilton TA, Billings JK. Cyclosporin improves psoriasis in a double-blind study. *JAMA* 1986;256:3110-16.
 33. Ellis CN, Fradin MS, Messana JM, Brown MD. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 1991;324:277-84.
 34. Joost T, van Bos JD, Heule F, Meinardi MMH. Low-dose cyclosporin A in severe psoriasis. A double-blind study. *Br J Dermatol* 1988;118:183-90.
 35. Christophers E, Mrowietz U, Henneicke HH, Farber L, Welzel D. Cyclosporine in psoriasis: a multicenter dose-finding study in severe plaque psoriasis. The German Multicenter study. *J Am Acad Dermatol* 1992;26:86-90.
 36. Finzi AF, Mozzanica N, Cattaneo A, Chiappino G, Pigatto PD. Effectiveness of cyclosporin treatment in severe psoriasis: a clinical and immunologic study. *J Am Acad Dermatol* 1989;21:91-7.
 37. Levell NJ, Shuster S, Munro CS, Friedmann PS. Remission of ordinary psoriasis following a short clearance course of ciclosporin. *Acta Derm Venereol* 1995;75:65-9.
 38. Buccheri L, Katchen BR, Karter AJ, Cohen SR. Acitretin therapy is effective for psoriasis associated with human immunodeficiency virus infection. *Arch Dermatol* 1997;133:711-5.
 39. Retinoids in psoriasis: disease management. *Drug Ther Perspect* 2002;18:11-15.
 40. Geilen CC, Arnold M, Orfanos CE. Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. *Br J Dermatol* 2001;144:583-6.
 41. Silvis NG, Levine N. Pulse dosing of tioguanine in recalcitrant psoriasis. *Arch Dermatol* 1999;135:433-7.
 42. Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German multicentre study. *Br J Dermatol* 1998;138:456-60.
 43. Magilavy D. Immunopharmacologic effects of Amevive (LFA 3-TIP) in chronic plaque psoriasis: selectivity for peripheral memory effector (CD45 RO+ over naïve (CD45 RA+) T cells. *Br J Dermatol* 1999;141:990(Abstr).
 44. Krueger JG, Walters IB, Miyazawa M, Gilleaudeau P, Hakimi J, Light S et al. Successful in vivo blockade of CD25 (high-affinity interleukin 2 receptor) on T cells by administration of humanized anti-Tac antibody to patients with psoriasis. *J Am Acad Dermatol* 2000;43:448-58.
 45. Abrams JR, Lebwohl MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS et al. CTLA4Ig-mediated blockade of T cell co-stimulation in patients with psoriasis vulgaris. *J Clin Invest* 1999;103:1243-52.
 46. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 2001;357:1842-7.
 47. Mease PJ, Goffe BS, Metz J, Vanderstoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis. *Lancet* 2000;356:385-90.
 48. Asadullah K, Sabat R, Wiese A, Docke WD, Volk HD, Sterry W. Interleukin-10 in cutaneous disorders: implications for its pathophysiological importance and therapeutic use. *Arch Dermatol Res* 1999;141:424-9.
 49. Balagon MV, Walsh DS, Tan PL, Cellona RV, Abalos RM, Tan EV et al. Improvement in psoriasis after intradermal administration of killed *Mycobacterium vaccae*. *Int J Dermatol* 2000;39:51-8.
 50. Mrowietz U, Graeber M, Brautigam M, Thurston M, Wagenaar A, Weidinger G et al. The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion. *Br J Dermatol* 1998;139:992-6.
 51. Zonneveld IM, Rubins A, Jablonska S, Dobzy A, Ruzicka T, Kind P et al. Topical tacrolimus is not effective in chronic plaque psoriasis. A pilot study. *Arch Dermatol* 1998;134:1101-2.
 52. Berth-Jones J, Todd G, Hutchinson PE, Thestrup-Pedersen K, Vanhoutte FP. The treatment of psoriasis with oral liarazole: a dose-ranging study. *Br J Dermatol* 2000;143:1170-6.
 53. Ellis CN, Varani J, Fisher GJ, Zeigler ME, Pershadsingh HA, Benson SC et al. Troglitazone improves psoriasis and normalizes models of proliferation skin disease: ligands for peroxisome proliferation activated receptor gamma inhibit keratinocyte proliferation. *Arch Dermatol* 2000;136:609-16.
 54. Richards HL, Fortune DG, Bowcock S. Cognitive-behavioural management of psoriasis. *Br J Dermatol* 1999;141:979 (Abstr).
 55. Shackley DC, Whitehurst C, Clarke NW, Betts C, Moore JV. Photodynamic therapy. *J R Soc Med* 1999;92:562-5.

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