Title
Update on Drugs Used in the Treatment of Psoriasis

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Update on drugs used in the treatment of psoriasis

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Introduction

Psoriasis is a chronic inflammatory skin disorder with intermittent flares and clearing that affects about 2% of the population. Psoriasis is an uncomfortable and occasionally disabling disease, with a social and economic impact that is often underestimated by medical personnel.

Psoriasis has several clinical phenotypes including guttate, pustular, and arthritic variants. This review focuses mainly on the most common form, chronic plaque psoriasis.

Clinical manifestations and history

Psoriasis can start at any time, but there are two main peaks of onset: young adults (16–22 years of age) and middle-aged adults (50–60 years of age).[1] Clinically the lesions are well demarcated with circumscribed, variably thickened, scaly plaques typically found on the elbows, knees, scalp, and sites of local trauma (Koebner's phenomenon). Relapses are common, and the frequency and severity of these episodes can be affected by exposure to exacerbating factors such as cold weather, dry humidity, infection and some drugs.

Heredity is an important factor in this disease and is probably polygenic. A study of several kindreds showed linkage to a gene localized to the distal end of chromosome 17q, but the biological effects of this gene remain to be elucidated.[2] The extent to which genetic and epigenetic factors are important is not yet understood.

Pathophysiological features

The characteristic histological features of psoriasis are hyperproliferation of the epidermis and the presence of inflammatory cells in the epidermis and dermis. In the psoriatic epidermis, the proliferative activity of keratinocytes is increased and the migration period of keratinocytes from the basal layer to the epidermal surface as well as the duration of the cell cycle is shortened.[3]

T-cell-produced cytokines are believed to be the inducing factors for the epidermal cell abnormalities in psoriasis.[4] Evidence for this is suggested by the therapeutic effectiveness of cyclosporin and the predominance of

CD4 lymphocytes in the dermis and CD8 cells in the epidermis of affected patients. It is not yet clear whether persistent T-cell activation is stimulated by a microbial antigen or an autoimmune process.[5]

Treatment

Psoriasis has no cure, only therapies that may clear lesions for variable periods of time. Many patients prefer treatment only with emollients and the avoidance of provoking factors. Local symptoms (pain, itching, or the reduction of manual dexterity due to hand involvement) or cosmetic concerns (prominent hand, leg or facial lesions) may lead the patient to seek therapy. The purpose of treatment is to minimize the severity of psoriasis so that it no longer interferes substantially with the patient's life. We encourage patients to accept some limited disease to minimize adverse effects from overly aggressive treatment.

Topical treatment

The initial treatment for limited psoriasis (less than 15–20% of the body surface affected) should be topical. The recognized methods of topical treatment are shown in Table 5.1.

Table 5.1 Topical therapy for chronic plaque psoriasis

Emollients
Keratolytic agents
Coal tar
Anthralin
Corticosteroids
Calcipotriene (calcipotriol)
Tazarotene

Emollients

Emollients may provide a weak but active treatment for psoriasis. These agents hydrate the hyperkeratotic surface of psoriatic plaques and may reverse the inflammatory consequences of a damaged stratum corneum. The most effective emollients such as petrolatum or aquaphor cream are greasy and sometimes disliked by patients.

Keratolytic agents

Keratolytic agents such as 2–10% salicylic acid may be used either alone or in combination with topical corticosteroids or coal tar. They soften the scale of psoriatic plaques facilitating their removal and increase the efficacy of combination treatments. Side-effects of salicylic acid include eye and skin irritation. No studies have documented the efficacy of keratolytics as single treatment agents for psoriasis and at best they are adjunctive forms of therapy.

Coal tar

Coal tar preparations infrequently clear psoriatic plaques when used alone. They are effective when used in combination with ultraviolet (UV) B phototherapy and their addition to shampoo preparations helps diminish psoriatic scaling of the scalp. Coal tar can cause an acneiform eruption or skin irritation and rarely, skin cancer induction has been reported.

Anthralin

Anthralin is used widely throughout Europe but only occasionally in the US. The Ingram regimen incorporates the 24-hour application of an anthralin paste, a daily coal tar bath and UVB phototherapy. The value of anthralin use remains to be proven as studies have shown that coal tar-UVB and coal tar-UVB-anthralin regimens are similar in terms of treatment speed, efficacy and cost.[6]

Anthralin irritates perilesional skin through the formation of free radicals and it is oxidized to colored products that may stain skin and fabrics. These side-effects can be limited by incorporating free-radical scavengers and antioxidants into the preparations.[7]

The current preferred method of anthralin use is a short-contact regimen in which anthralin is applied for 0.5 to 1 hour before removal. This allows penetration of only lesional skin,[8] limiting side-effects while maintaining efficacy. This is a moderately effective treatment but not as good as potent topical corticosteroids. When effective, anthralin may provide a longer disease-free period than topical steroids.

Corticosteroids

Topical corticosteroids are easy to use and have short-term efficacy. The more potent topical corticosteroids are consistently effective and are the initial choice of therapy by two-thirds of dermatologists in the United States.[9]

The many available corticosteroids differ in efficacy and are ranked by a potency class system. Once-daily topical corticosteroid use may be as effective as traditional twice-daily treatment with fewer side-effects.

Short term use provides minimal risk but prolonged therapy may result in thinning and pigmentary change of the skin, striae, and tachyphylaxis (tolerance to the action of the treatment). By 3–6 months after steroid-induced clearing, 50% or more of patients have relapsed with or without continuing use of steroids.[9] Steroids may also render the psoriasis unstable and occasionally a severe pustular variant may result. Topical corticosteroid efficacy can be improved by occlusion under a plastic film, but this increases the risk of side-effects. Pituitary–adrenal suppression can be induced in adults with daily use of 30 g or more of 0.025% betamethasone valerate cream under occlusion[10] and in infants even 1% hydrocortisone cream may result in a similar effect.[11]

Calcipotriene

Calcipotriene (in some countries, calcipotriol) is a topically applied vitamin D derivative. Studies have shown that the efficacy of calcipotriene ointment is similar to that of a mid-potency topical steroid, 0.1% betamethasone valerate.[12] Long-term continuous therapy with calcipotriene for up to 12 months has been shown to result in consistent improvement.[13] This ointment causes appreciable irritation in some patients, especially on the face or genital area.

Topical retinoids

Recent research has show that a unique retinoid molecule, tazarotene, can work topically with an acceptable minimal toxicity. Tazarotene used as a 0.05% or 0.1% gel can produce 50–100% improvement in approximately 70% of patients.[14,15] Burning, irritation and redness occur in 10–20% of patients but can be mitigated by emollients or topical steroids. Adjunctive use with mid- or high-potency steroids or calcipotriene may enhance the efficacy of tazarotene treatment.[16] There are reports of a treatment response remaining up to 3 months after active treatment with tazarotene has been discontinued.[17] The drug was approved in the US and many European countries in 1997–1998.

Table 5.2 Phototherapy and systemic therapies for moderate to severe psoriasis

Phototherapy (UVB +/– Tar)
Photochemotherapy (PUVA)
Methotrexate
Retinoids
Cyclosporin

Phototherapy and systemic treatments for moderate to severe psoriasis

Indications for more aggressive treatment include the involvement of large areas (more than 20% of the body surface) where topical treatment is impractical, a poor response to topical therapy, or psoriasis that is psychologically limiting or occupationally disabling. The choices are phototherapy, systemic drug therapy or a combination of these modalities (Table 5.2). All these modalities have potential toxicity, and the benefit/risk ratio of each must be periodically evaluated to avoid excessive toxicity.

Phototherapy (UVB radiation)

UVB radiation utilizes wavelengths of 280 to 320 nm and, in combination with coal tar preparations (the Goeckerman regimen), is the safest option for

people with moderate-to-severe disease as the risks are limited to a very small increase in skin cancer induction.

Crude coal tar 1% in a hydrophilic ointment is applied for 2–10 hours then washed off prior to UVB treatments which are given up to two times each day. If the tar is not washed off, it can act as a UVB blocker. This treatment leads to substantial improvement in psoriasis in at least 80% of patients.[18] Approximately 30 treatments are needed to obtain a reasonable response. Intensive treatment with UVB phototherapy and coal tar in an inpatient setting is rapidly effective within 2 to 3 weeks. Remission can be maintained by intermittent UVB phototherapy. Outpatient treatment is also effective although generally less rapid. UVB phototherapy without coal tar is used regularly only in patients with guttate psoriasis but in this situation it can achieve a rapid response.

Recently, several UVB phototherapy variations have been studied including narrow-band UVB (311 nm)[19] and individual psoriasis plaque irradiation with a 308 nm excimer laser.[20] It has been proposed that these modifications may make this modality even safer by limiting UV exposure. However, the efficacy of these modalities remains to be proven.

Photochemotherapy (PUVA)

The second form of UV therapy, photochemotherapy, combines methoxsalen, a photosensitizing drug, with UVA phototherapy in the range of 320–400 nm.[21] Methoxsalen is administered 1–2 hours prior to light exposure in a dosage of 0.4–0.6 mg/kg body weight. The dosage of UVA is determined by the patient's skin type. Peak erythema occurs at approximately 48 hours post-treatment and thus treatments may be repeated up to two or three times weekly (more frequent treatments would increase the risk of burning). The mechanisms of action of PUVA have not been definitively elucidated but theories include: (a) a suppressive action on cell-mediated immune responses in the skin and (b) the intercalation of methoxsalen into DNA, resulting in crosslinks that interfere with DNA synthesis and block cell proliferation.[21,22]

PUVA is a highly effective treatment, which provides resolution of skin lesions after 20 to 30 treatments in over 85% of patients.[19,23] Maintenance can often be achieved with treatment as little as once every 2 to 4 weeks, which can be tapered to eventual discontinuation of treatment. The duration of remission ranges from 6 to 12 months. Topical or bath applications of methoxsalen have been utilized, but there is an increased risk of skin burning.

PUVA patients may report nausea, burning, and pruritus. Long-term risks include an increase in skin cancer and photodamage. The frequency of squamous cell carcinomas of the skin is increased in PUVA patients, most significantly after 160 treatments. There is an increased risk of genital cancer if this area is not shielded. A

small incidence of melanomas was found in a population of patients treated with PUVA for over 20 years.[24] This finding raises a concern about the amount of PUVA patients can safely receive and the importance of following these patients carefully. Benign and premalignant keratoses, irregular pigmentation and wrinkling can also be induced with intensive PUVA therapy.

If treatment is limited to less than 160 treatments, the risk of skin cancer or photodamage is limited and the therapeutic index of this treatment is high.[25] PUVA can be combined with an oral retinoid to minimize radiation exposure but it is uncertain whether this decreases the incidence of photodamage or skin cancers.

Methotrexate

Methotrexate is a folic acid antagonist and the gold standard for effective therapy of patients with moderate-to-severe psoriasis. Methotrexate may be the next choice in severe psoriatics if phototherapy or PUVA is discontinued because of long-term usage, intolerable side-effects, a limited response or inconvenience. Methotrexate blocks DNA synthesis resulting in the inhibition of cell proliferation in rapidly dividing tissues such as the hyperproliferative psoriatic epidermis and normal gastrointestinal and germinative epithelium.[26] It is also thought to have an immunosuppressive effect on mononuclear cells in the skin, blood, and lymphatic tissues.[27]

Methotrexate is most commonly administered orally in three doses (usually 2.5 to 5 mg each) at 12-hour intervals.[28] This regimen is repeated once weekly and can inhibit the replication of hyperproliferative cells with minimal side-effects. This dosing regimen is preferred by 70% of dermatologists.[29] An alternative is an oral or parenteral dose of methotrexate given once weekly. For this regimen, the usual dosage in a 70 kg adult is 10 to 25 mg/week.

The guidelines for methotrexate use were updated in 1998.[30] Patients must have normal renal function, blood cell counts, and liver function. Since 85% of methotrexate is excreted through the kidneys, patients with poor renal function may have sustained increases in plasma drug concentrations resulting in side-effects similar to a drug overdose, including cutaneous or gastrointestinal erosions and leukopenia.

The development of hepatic fibrosis or cirrhosis is the major long-term side-effect of methotrexate and thus this medication should not be used in patients with a history of abnormal liver function or excessive alcohol intake. In studies of psoriatic patients with a cumulative methotrexate dose of 1.5 g or less, approximately 3% develop cirrhosis. The proportion increases to 20 to 25% among patients who have received 4 g or more of methotrexate.[30] We believe that methotrexate-related liver disease occurs less frequently than previously reported, possibly because of improved patient selection and the use of rotation

of additional therapies for extensive psoriasis.

Standard tests of liver function and imaging procedures do not reliably identify cirrhosis. However, liver function tests should be done initially and at intervals of 2–3 months, as they are relatively inexpensive and may be helpful. The 1998 methotrexate guidelines[30] recommend that if there are no hepatic risk factors prior to therapy, a liver biopsy should be performed indefinitely after each 1.5 g of cumulative drug use. If liver risk factors are present when starting therapy, a liver biopsy should be done at or soon after the start of therapy. If fibrosis is found, the drug should be stopped even though methotrexate-related cirrhosis is of low aggressiveness and may not progress with continued treatment.[31] The drug can be re-started in the future with careful observation. Drug dosage should be constantly titrated so that the smallest effective amount is used, and the goal of improvement should not be complete clearance of skin lesions as this may require aggressive and thus, risky dosing.

Retinoids

Retinoids alone have limited effectiveness in psoriatic patients except in specialized cases. Only half of patients with extensive plaque psoriasis will achieve a 75% reduction in skin lesional area with the use of retinoids.[32] Acitretin, which recently replaced the almost identical etretinate, is most useful in patients with erythrodermic and acral localized psoriasis and in HIV-positive patients in whom UV therapy may increase T-cell suppression or virus activation. For generalized pustular psoriasis, both acitretin and isotretinoin (a better choice in women with child-bearing potential because of a shorter half-life) can produce rapid improvement and are extremely valuable treatment options.[33]

The mechanism for psoriatic improvement with retinoids may derive from their ability to stimulate epithelial differentiation. Retinoids activate and repress genomic function resulting in altered protein expression, which in turn affects clinical disease. Further, they replete the diminished number of Langerhans cells in psoriatic lesions and increase delayed hypersensitivity.

Acitretin should be started at a low dose (i.e. 0.3 to 0.4 mg/kg per day) to minimize flares and side-effects.[34] If required, this can be gradually increased. Acitretin therapy may be associated with many side-effects including skin dryness and erythema. Liver function tests and triglyceride levels may become elevated with treatment and thus should be checked prior to therapy and then at intervals of 1–2 months.

Because these drugs are teratogenic, pregnancy must be avoided during treatment and for at least 3 years following cessation of treatment. Acitretin is a clinically active metabolite of etretinate and in combination with alcohol, is converted back to

etretinate which has a longer elimination half-life[35] and prolonged teratogenic potential. Thus, alcohol must not be consumed by patients on acitretin during treatment or for 2 months following discontinuation of treatment.

After 1 to 2 years of systemic retinoid therapy in high dosage, skeletal abnormalities, including ligamentous ossification and periosteal new bone formation, may occur in some patients.[36] Acitretin can be combined with PUVA to limit the dosage and thus the side-effects of both these therapeutic options.

Cyclosporin

Cyclosporin is a relatively new treatment for extensive psoriasis and may be used in patients refractory to all other treatments.[37] Cyclosporin blocks production of a calcineurin-dependent factor essential for transcription of the interleukin-2 gene which in turn blocks the proliferation of activated T-cells and the production of their cytokines[38,39] thought to induce the psoriatic phenotype.

About 90% of patients respond to low doses of cyclosporin (Sandimmune or Neoral, 2 to 5 mg/kg per day, depending on which preparation is used) within 1 to 3 months. Once optimal improvement is reached, maintenance therapy is usually required although lower doses may be utilized.[40] It is recommended that cyclosporin should be given for no more than 1 year. Most patients relapse in 2 to 4 months if the dosage is decreased too low.

Cyclosporin may find great value in the initial treatment of acute, severe disease minimizing the need for hospitalization.[41] However, it may be associated with significant side-effects including hypertension and potentially irreversible impairment of renal function. Because cyclosporin is an immunosuppressive agent, there is an unproven possibility of an increased risk of cancer. Thus, it is wise to avoid combining cyclosporin treatment with phototherapy or other potentially mutagenic treatments. In the author's opinion, it will be important to find ways to rotate patients from cyclosporin after a few months to safe long-term treatments such as methotrexate or PUVA.

Systemic corticosteroids

Oral corticosteroid therapy is effective, but is associated with many side-effects. Psoriasis may worsen significantly after corticosteroid therapy is stopped, and occasionally a severe, treatment-resistant pustular form may develop. This treatment should be reserved for acutely ill patients with erythrodermic psoriasis and should be given for only a short period.

Therapeutic strategies

Several variables must be considered when selecting therapy for a patient with moderate-to-severe psoriasis including the patient's health and need for aggressive therapy, the patient's

response to previous treatment, the therapeutic options available to the physician, and the patient's preferences. All treatments have side-effects, which must be suited to the patient, and certain variants of psoriasis require specialized treatment. The best strategy for long-term safety in treating psoriasis may be to rotate therapeutic regimens periodically before toxicity from any one modality becomes evident.[42]

Future treatments

Recent research has revealed a likely etiologic role for T cells in psoriasis and thus immunotherapy has been of interest. Anti-CD4 monoclonal antibodies have been used with limited success to treat a small number of patients and many immunomodulating drugs are being tested.[43,44] Attempts to identify the gene alterations responsible for psoriasis may soon be successful and gene therapy may be available in the future.

References

1. Lomholt G, Psoriasis: prevalence, spontaneous course and genetics: a census study on the prevalence of skin diseases on the Faroe Islands. Copenhagen, Denmark: GEC GAD, 1963.

2. Tomfohrde J, Silverman A, Barnes R et al, Gene for familial psoriasis, susceptibility mapped to the distal end of human chromosome 17q. *Science* 1994: 264; 1141–5.

3. Weinstein GD, McCullough JL. Ross PA. Cell kinetic basis for pathophysiology of psoriasis. *J Invest Dermatol* 1985: 85; 579–83.

4. Baker BS, Swain AF, Valdimarsson H, Fry L, T-cell subpopulations in the blood and skin of patients with psoriasis. *Br J Dermatol* 1984: 110; 37–44.

5. Cooper KD, Skin-infiltrating lymphocytes in normal and disordered skin activation signals and functional roles in psoriasis and mycosis fungoides type cutaneous T cell lymphoma. *J Dermatol* 1992: 19; 731–7.

6. Ashton RE, Andre P, Lowe NJ, Whitefield M, Anthralin: historical and current perspectives. *J Am Acad Dermatol* 1983: 9; 173–92.

7. Finnen MJ, Lawrence CM, Shuster S, Inhibition of dithranol inflammation by free-radical scavengers. *Lancet* 1984: 2; 1129–30.

8. Lowe NJ, Ashton RE, Koudsi H et al, Anthralin for psoriasis: short-contact anthralin therapy compared with topical steroid and conventional anthralin. *J Am Acad Dermatol* 1984: 10; 69–72.

9. Liem W, McCullough JL, Weinstein GD, Effectiveness of topical therapy for psoriasis: results of a national survey. *Cutis* 1995: 55; 306–10.

10. James VH, Munro DD, Feiwel M, Pituitary-adrenal function after occlusive topical therapy with betamethasone-17-valerate. *Lancet* 1967: 2; 1059–61.

11. Turpeinen M, Absorption of hydrocortisone from the skin reservoir in atopic dermatitis. *Br J Dermatol* 1991: 124: 358–60.

12. Kragballe K, Gjertsen BT, De Hoop D et al, Double-blind, right/left comparison of

calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet* 1991: 337; 193–6.

13. Ramsay CA, Berth-Jones J, Brandin G et al, Long term use of topical calcipotriol in chronic plaque psoriasis. *Dermatology* 1994; 189; 260–4.

14. Weinstein GD, Tazarotene gel: efficacy and safety in plaque psoriasis. *J Am Acad Dermatol* 1997: 37; S33–8.

15. Weinstein GD, Krueger CG, Lowe NJ et al, Tazarotene gel, a new retinoid, for topical therapy of psoriasis; vehicle-controlled study of safety, efficacy and duration of therapeutic effect. *J Am Acad Dermatol* 1997: 37; 85–92.

16. Guenther L, Tazarotene combination treatments in psoriasis. *J Am Acad Dermatol* 2000; 43; S36–42.

17. Lebwohl M, Ast E, Callen JP, Once-daily tazarotene gel versus twice-daily fluocinonide cream in the treatment of plaque psoriasis. *J Am Acad Dermatol* 1998; 38: 705–11.

18. Stern RS, Armstrong RB, Anderson TF et al, Effect of continued ultraviolet B phototherapy on the duration of remission of psoriasis: a randomized study. *J Am Acad Dermatol* 1986: 15; 546–52.

19. Gordon PM, Diffey BL, Mathews JNS, Farr PM, A randomized comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *J Am Acad Dermatol* 1999: 41: 728–32.

20. Asawonda P, Anderson RR, Chang Y, Taylor CR, 308-nm excimer laser for the treatment of psoriasis: a dose-response study. *Arch Dermatol* 2000: 136; 619–24.

21. Pathak MA, Fitzpatrick TB, Parrish JA, Pharmacologic and molecular aspects of psoralen photochemotherapy. In: Farber E, Cox AJ, Jacobs PH, Nall ML (eds) *Psoriasis: proceedings of the Second International Symposium*. New York: Yorke Medical Books, 1977, pp. 262–71.

22. Kripke ML, Morison WL, Parrish JA, Systemic suppression of contact hypersensitivity in mice by psoralen plus UVA radiation (PUVA). *J Invest Dermatol* 1983: 81; 87–92.

23. Melski JW, Tanenbaum L. Parrish JA et al, Oral methoxsalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. *J Invest Dermatol* 1977: 68; 328–35.

24. Stern RS, Nichols KT, Vakeva LH, Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-up Study. *New Engl J Med* 1997: 336; 1041–5.

25. Stern RS, Laird N, Melski J et al, Cutaneous squamous-cell carcinoma in patients treated with PUVA. *N Engl J Med* 1984: 310; 1156–61.

26. McCullough JL, Weinstein GD, The action of cytotoxic drugs on cell proliferation in psoriasis. In: Wright NA, Camplejohn RS (eds) *Psoriasis: cell proliferation*. Edinburgh: Churchill Livingstone, 1983, pp. 347–54.

27. Jeffes EWB III, McCullough JL, Pittelkow MR et al, Methotrexate therapy of psoriasis: differential sensitivity of proliferating lymphoid and epithelial cells to the cytotoxic and growth-inhibitory effects of methotrexate. *J Invest Dermatol* 1995: 105; 183–8.

28. Weinstein GD, Frost P, Methotrexate for psoriasis: a new therapeutic schedule. *Arch Dermatol* 1971: 103; 33–8.

29. Peckham PE, Weinstein GD, McCullough JL, The treatment of severe psoriasis: a national survey. *Arch Dermatol* 1987: 123; 1303–7.

30. Roenigk HH, Auerbach R, Maibach H et al, Methotrexate in psoriasis: consensus conference. *J Am Acad Dermatol* 1998: 38; 478–85.

31. Zachariae H, Methotrexate side-effects. *Br J Dermatol* 1990: 122 (Suppl 36); 127–33.

32. Gollnick HPM, Orfanos CE, Clinical efficacy of etretinate and acitretin: European experience. In: Roenigk HH Jr, Maibach HI (eds) *Psoriasis, 2nd edn.* New York: Marcel Dekker, 1991, pp. 725–48.

33. Moy RL, Kingston TP, Lowe NJ, Isotretinoin vs etretinate therapy in generalized pustular and chronic psoriasis. *Arch Dermatol* 1985: 121; 1297–301.

34. Ling MR, Acitretin: optimal dosing strategies. *J Am Acad Dermatol* 1999: 41; S13–17.

35. Larsen FG, Jakobsen P, Knudsen J et al, Conversion of acitretin to etretinate in psoriatic patients is influenced by ethanol. *J Invest Dermatol* 1993: 100; 623–7.

36. DiGiovanna JJ, Helfgott RK, Gerber LH, Peck GL, Extraspinal tendon and ligament calcification associated with long-term therapy with etretinate. *N Engl J Med* 1986: 315; 1177–82.

37. Ellis CN, Fradin MS, Messana JM et al, Cyclosporine for plaque-type psoriasis: Results of a multidose, double-blind trial. *N Engl J Med* 1991: 324; 277–84.

38. Wong RL, Winslow CM, Cooper KD, The mechanism of action of cyclosporin A in the treatment of psoriasis. *Immunol Today* 1993: 14; 69–74.

39. O'Keefe SJ, Tamura J, Kincaid RL et al, FK-506- and CsA-sensitive activation of the interleukin-2 promoter by calcineurin. *Nature* 1992: 357; 692–4.

40. Shupack J, Abel E, Bauer E et al, Cyclosporine as maintenance therapy in patients with severe psoriasis. *J Am Acad Dermatol* 1997: 36; 423–32.

41. Koo J, Cyclosporine in dermatology. Fears and opportunities. *Arch Dermatol* 1995: 131; 842–5.

42. Weinstein GD, White GM, An approach to the treatment of moderate to severe psoriasis with rotational therapy. *J Am Acad Dermatol* 1993: 28; 454–9.

43. Owen CM, Harrison PV, Successful treatment of severe psoriasis with basiliximab, an interleukin-2 receptor monoclonal antibody. *Clin Exp Dermatol* 2000: 25; 195–7.

44. Grundmann-Kollmann M, Mooser G, Schraeder P et al, Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J Am Acad Dermatol* 2000: 42; 835–7.