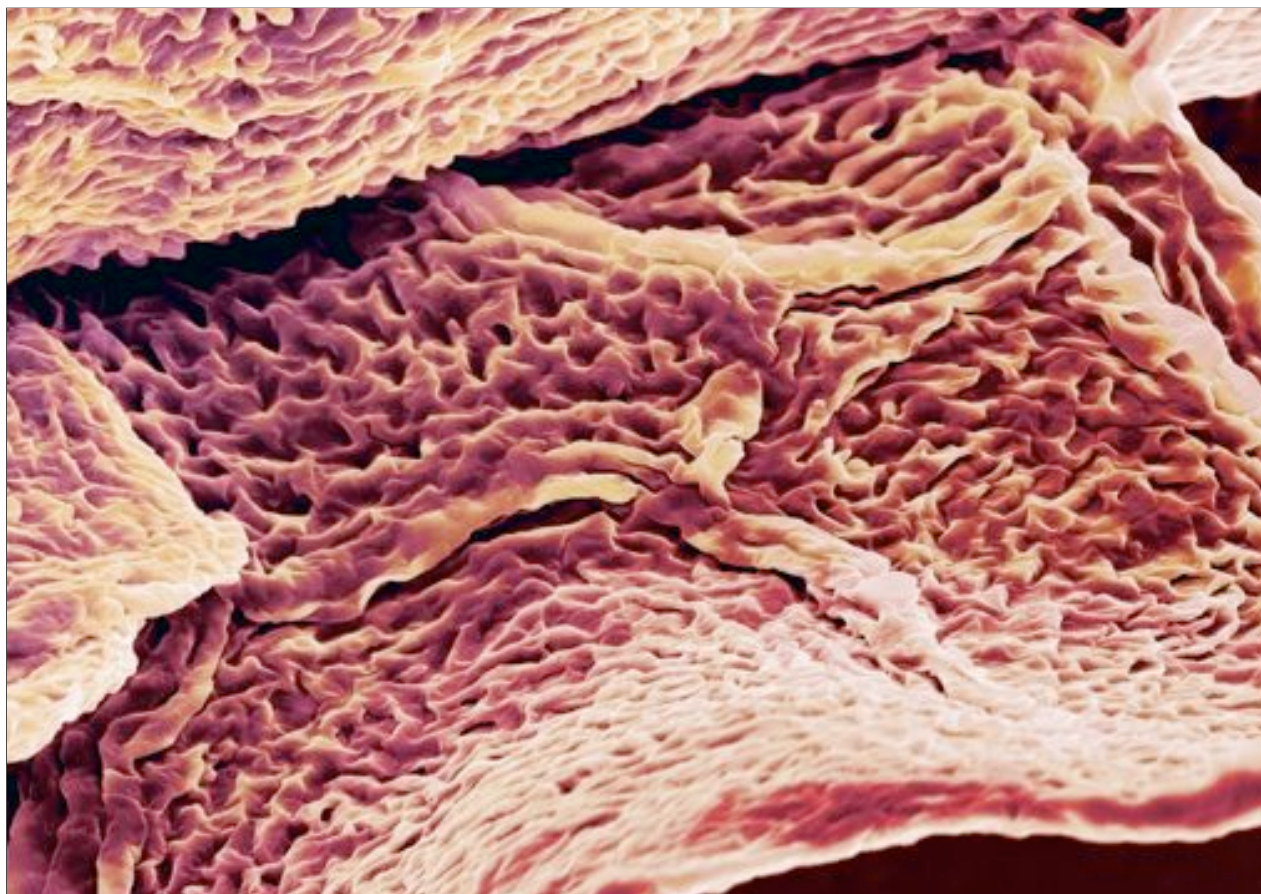


Current treatment options in the management of psoriasis

Eleanor Higgins MB BCh, BAO, MRCPI and Trevor Markham MD, BAO, MRCPI



TdS

Psoriasis is a common chronic condition and treatment choice primarily centres on disease severity. Our Drug review considers the therapeutic options, their properties and safety profiles, followed by sources of further information and an analysis of prescription data.

Psoriasis is a chronic inflammatory condition that can cause significant discomfort, disfigurement and psychological distress for patients. Fewer than half of those affected by psoriasis find their treatment highly satisfactory. Although there is no cure for psoriasis,

numerous topical and systemic therapies are available with comprehensive guidelines for these available on the British Association of Dermatologists (BAD) website at www.bad.org.uk.

Therapeutic modalities are often selected on the basis of disease severity, patient preference, relevant co-morbidities and efficacy. For most patients, the initial treatment plan centres on disease severity and it may be useful to consider patients as having either mild-to-moderate or moderate-to-severe disease. Mild-to-moderate psoriasis may often be managed by topical therapy, while more severe disease may require systemic therapy. Psoriasis involving the hands, feet and face may result in more functional debilitation and greater impact on quality of life and warrant more aggressive therapeutic approaches.

Treatment regimens may clear the skin but recurrences are frequent and many patients require repeat treatment. This emphasises the importance of considering the risk-benefit profiles of proposed therapies.

Topical therapy

Topical corticosteroid therapy can be of benefit in the treatment of psoriasis in certain sites such as the scalp, palms and soles. Corticosteroids range in potency from very mild 1 per cent hydrocortisone to very potent clobetasol propionate. Their use has been limited by adverse effects, which include skin atrophy, striae, purpura, skin fragility, telangiectasia and tachyphylaxis. Nevertheless topical corticosteroids are very useful for the treatment of psoriasis of the scalp, palms and soles (see Figure 1) where the thicker skin is more resistant to these adverse effects.

Tar has been used in the treatment of psoriasis for many years, usually combined with UV phototherapy. In 1925, Goeckerman introduced daily crude coal tar with UVB phototherapy for generalised psoriasis and this treatment was widely used.¹ Bed shortages and lack of cosmetic appeal have limited patients' use of tar-containing agents.

Dithranol is another topical therapy with a long history in psoriasis. The standard dithranol regimen is to apply increasing concentrations (0.05-2 per cent) on a daily basis. This therapy is particularly useful for chronic plaque psoriasis (see Figure 2) but is not recommended for acute forms of the disease.² Dithranol is also used in combination with UV phototherapy to improve efficacy and limit side-effects.

Topical vitamin D analogues are effective in psoriasis. In a six-week multicentre trial, calcipotriol was more effective than the topical corticosteroid fluocinonide (Metosyn) in plaque psoriasis.³ Calcitriol (Silkis)⁴ and tacalcitol (Curatoderm)⁵ have also been shown to be effective in psoriasis, with calcitriol thought to be less irritant on the face and intertriginous sites.

These agents can cause local irritation and excessive use can lead to hypercalcaemia.⁶ This has led to the use of combinations of vitamin D analogues with other topical therapies, UV phototherapy and systemic therapies. Topical retinoids are another treatment option for mild-to-moderate psoriasis.⁷

Phototherapy

Broadband UVB has been used since the early 20th century, but the spectrum of light that is most effective for clearing psoriasis is in the narrow range around 311nm (see Figure 3). Bulbs that have an out-



Figure 1. The use of topical steroids is limited by adverse effects; however, they are useful in treating areas of the body where the skin is thicker, such as the palms

put in this range have been developed and are used in narrowband UVB (nUVB) therapy. nUVB therapy (311-313nm) is more effective than conventional broadband UVB with respect to clearing times and remission.⁸ Treatment schedules are similar for both, with nUVB administered three times per week. This form of phototherapy is less erythemogenic than broadband UVB and has mainly replaced it as first-line phototherapy for psoriasis.

The efficacy of nUVB compared to photochemotherapy (PUVA) has also been demonstrated.⁹ In comparison to PUVA, nUVB-treated patients do not have to take tablets or wear protective eyewear. It can also be used during pregnancy and in children. Long-term safety data are awaited but nUVB is thought to be less carcinogenic than PUVA.¹⁰

Remission is variable and patients may require repeat courses. This becomes particularly relevant when one considers the risk of nonmelanoma skin cancers associated with prolonged PUVA therapy.¹¹ As a result of this concern PUVA therapy is often combined with other treatments such as retinoids and vitamin D analogues to reduce the number of exposures required for clearance.

A laser that emits at a wavelength of 308nm is a new therapeutic modality that has been found to be safe and effective in psoriasis in a multicentre study.¹² Compared to conventional phototherapy it has the advantage of targeting only affected skin and thus reduces the risks to uninvolved skin.

Systemic therapy

Antimetabolites

Methotrexate is an antimetabolite agent that has been used for many years in psoriasis treatment and remains one of the most effective therapies.¹³ Methotrexate is indicated for recalcitrant disease unresponsive to topical or phototherapy and is particularly useful if the patient has an associated arthropathy. It is usually given orally once a week and folic acid supplements can be given to reduce nausea associated with this agent.

Contraindications include liver abnormalities, poor renal function, anaemia, thrombocytopenia, gastritis, active infection and high alcohol intake.¹⁴ Long-term use of methotrexate is associated with liver toxicity so regular liver function tests are required and also regular full blood counts to monitor marrow toxicity.

Oral retinoids

Oral retinoids are potent antipsoriatic drugs for pustular and erythrodermic psoriasis but are less effective in chronic plaque psoriasis.¹⁶

Acitretin is given in a dose of 0.3-0.6mg per kg per day, once or twice daily with meals, for 6-12 weeks. Combination therapy with PUVA and UVB allows dose reduction and decreases the incidence of adverse effects. These may include mucocutaneous dryness, alopecia, elevated serum lipids and liver function tests, hyperostosis and teratogenicity. As a result the package insert recommends that acitretin should not be given

to women of child-bearing potential who may become pregnant within three years. Despite these adverse effects acitretin is a safe treatment for psoriasis.

Immunosuppressors

Ciclosporin was developed as an immunosuppressive transplantation drug in the early 1970s. Its efficacy in psoriasis was first described in 1979.¹⁷ The long-term risks of therapy include nephrotoxicity¹⁸ and hypertension. However, ciclosporin is excellent for short-term use due to its weak myelosuppressive effect in comparison to methotrexate. Hypertension can be treated with calcium-channel blockers and this has been shown to prevent loss of renal function.¹⁹

Other immunosuppressive agents have been tried in psoriasis with mixed results, either due to lack of efficacy or the development of adverse effects. Hydroxycarbamide is an effective therapy for chronic plaque psoriasis whose main adverse effect is bone marrow toxicity (unlicensed indication).²⁰ Mycophenolate mofetil is a immunosuppressive transplantation agent that is safe and effective for severe psoriasis using a dose of 2g per day (unlicensed indication).²¹

Fumaric acid derivatives (unlicensed indication) are widely used for psoriasis in some European countries. Four months' treatment with fumaric acid derivatives in one trial resulted in efficacy in 80 per cent of patients, although adverse effects such as GI upset, flushing and lymphocytopenia occurred in 67 per cent of patients.²²

Biologics

The failure of patients to respond to or to tolerate the above treatment modalities has led to the search for better therapies and recently so-called 'biological therapies' have been developed. Biologic therapies are immunomodulators that target specific molecular steps in the pathogenesis of psoriasis, interfering with T-cell function and cytokine activity.

Tumour necrosis factor (TNF) is a proinflammatory cytokine that plays a central role in the pathogenesis of psoriasis, psoriatic arthritis and other inflammatory diseases. There are three approved agents that target TNF: anti-TNF alpha monoclonal antibodies adalimumab (Humira) and infliximab (Remicade) and a soluble TNF-alpha receptor fusion protein, etanercept (Enbrel).

To be considered eligible to receive a biologic agent under BAD guidelines, patients should have severe psoriasis, defined by a PASI (psoriasis area and severity index score) of 10 or more, have severe,



Figure 2. Dithranol is particularly useful in the treatment of chronic plaque psoriasis and can be used in combination with UV phototherapy to improve outcomes and limit side-effects



Figure 3. Narrowband UVB is first-line phototherapy for the treatment of psoriasis and is more effective than broadband UVB and comparable to PUVA with respect to clearance times and remission

unstable or life-threatening disease and be ineligible for phototherapy or standard systemic therapy because of contraindications, intolerance or unresponsiveness to treatment.²³

Adalimumab is a fully humanised IgG1 monoclonal antibody for used in moderate-to-severe psoriasis. It has shown to be highly effective in three large randomised controlled trials (RCTs).²⁴ Onset is rapid – after 12 weeks in one trial, 53 per cent of patients on adalimumab 40mg every two weeks and 80 per cent on 40mg weekly achieved a 75 per cent reduction in PASI (PASI 75) score.²⁵ The National Institute for Health and Clinical Excellence (NICE) has approved the use of adalimumab (40mg every two weeks) in severe plaque psoriasis, with continued therapy subject to adequate response at 16 weeks.²⁶

Infliximab is a chimeric monoclonal anti-TNF antibody and is also highly effective in the treatment of

chronic plaque psoriasis.²⁴ Infliximab has a rapid onset of action, with 79 per cent of patients achieving a PASI 75 by week 10, with a sustained response in a high percentage of patients at one year. Loss of efficacy correlates with development of antibodies, which occurs in 19 per cent of patients treated with infliximab.²⁷

NICE recommends infliximab to be commenced at initially 5mg per kg² at weeks 0, 2 and 6 and then every eight weeks. Treatment beyond 10 weeks is only recommended in patients who achieve certain response criteria.

Etanercept, a TNF-alpha receptor fusion protein, has been shown to be effective in the treatment of chronic plaque psoriasis in three large RCTs.²⁸ Onset of action appears to be slower than with the monoclonal antibodies. Action appears dose related and overall 34 per cent of patients receiving 25mg etanercept twice weekly achieved PASI 75 after 12 weeks, compared with 49 per cent of patients on 50mg twice weekly.²⁹

Recent BAD guidelines recommend that etanercept be commenced at 50mg weekly or 25mg twice weekly with disease response to be assessed at three to four months. In patients who respond, therapy may be continued according to clinical need, but long-term data on efficacy are limited to two years.²⁹ Some smaller studies suggest that its efficacy may be improved by the addition of methotrexate³⁰ or acitretin.

Ustekinumab (Stelara) is a fully human IgG1 K monoclonal antibody that targets the p40 subunit of interleukins IL-12 and IL-23. These cytokines play a role in regulation of immune response and T-cell activation in psoriasis. Ustekinumab is licensed for use in patients with moderate-to-severe psoriasis at 45mg (or 90mg if >100kg) at weeks 0 and 4 and then 12 weekly thereafter.

It has shown to be highly effective in the treatment of chronic plaque psoriasis, both at 45mg and 90mg, and its onset of action is evident within two weeks. By 12 weeks, 67 per cent of patients receiving a dose of 45mg and 72 per cent of those receiving 90mg achieved PASI 75. Maximal efficacy is evident between weeks 20 and 24. Factors predictive of a poorer response include higher body weight, previous poor response to at least one biologic agent, longer duration of psoriasis and a history of psoriatic arthritis.³¹

NICE has approved the use of ustekinumab in patients with severe plaque psoriasis, with treatment to be continued beyond 16 weeks only in those who respond.³² In the light of limited patient exposure,

ustekinumab should be reserved for use in patients with severe psoriasis and where TNF antagonist therapy has failed or is contraindicated.³⁰

Potential adverse effects of TNF antagonist therapy include infections, reactivation of tuberculosis, development of demyelinating disease and worsening of cardiac failure. The BAD Biologic Interventions Registry (BAD-BIR) has been established in the UK to collect long-term safety data. This registry aims to follow up all patients on biologic therapy for five years, together with 4000 control subjects on conventional second-line drugs for psoriasis.²³

Etanercept or adalimumab are appropriate for patients with stable chronic plaque psoriasis, based on favourable risk/benefit profile and ease of administration. Where rapid disease control is required, adalimumab or infliximab may be more suitable due to early onset of action and a high chance of achieving a significant improvement in PASI 75 by three months.³³ Treatment decisions around biologics are complex and patients who have failed treatment with one or more biologic may respond to another.³⁴

Conclusion

Psoriasis is a common chronic condition and has been shown to significantly influence a patient's quality of life. Topical treatments remain the mainstay of therapy in psoriasis, with 70-80 per cent of all patients with psoriasis responding adequately to topical treatments. Vitamin D₃ analogues such as calcipotriol and in combination with a corticosteroid are increasingly preferred as first-line topical therapy by patients for convenience and ease of use. Newer systemic agents such as fumaric ester derivatives with less adverse effects and improved patient tolerability are being used successfully.

Recent advances in our understanding of its pathophysiology have led to the emergence of biologic agents that specifically target key mechanisms in the pathogenesis of psoriasis. These biologics have led to dramatic clinical responses in patients with psoriasis, and some appear to be more efficacious than older systemic therapies. However, their exact role in the management of psoriasis remains to be fully established, especially as long-term safety data are awaited on the newer biologic agents.

References

1. Thami GP, *et al.* *Clin Exp Dermatol* 2002;27(2):99-103.
2. Mahrle G. *Clin Dermatol* 1997;15(5):723-37.
3. Bruce S, *et al.* *J Am Acad Dermatol* 1994;31:755-9.
4. Langner A, *et al.* *Br J Dermatol* 1996;135:385-9.

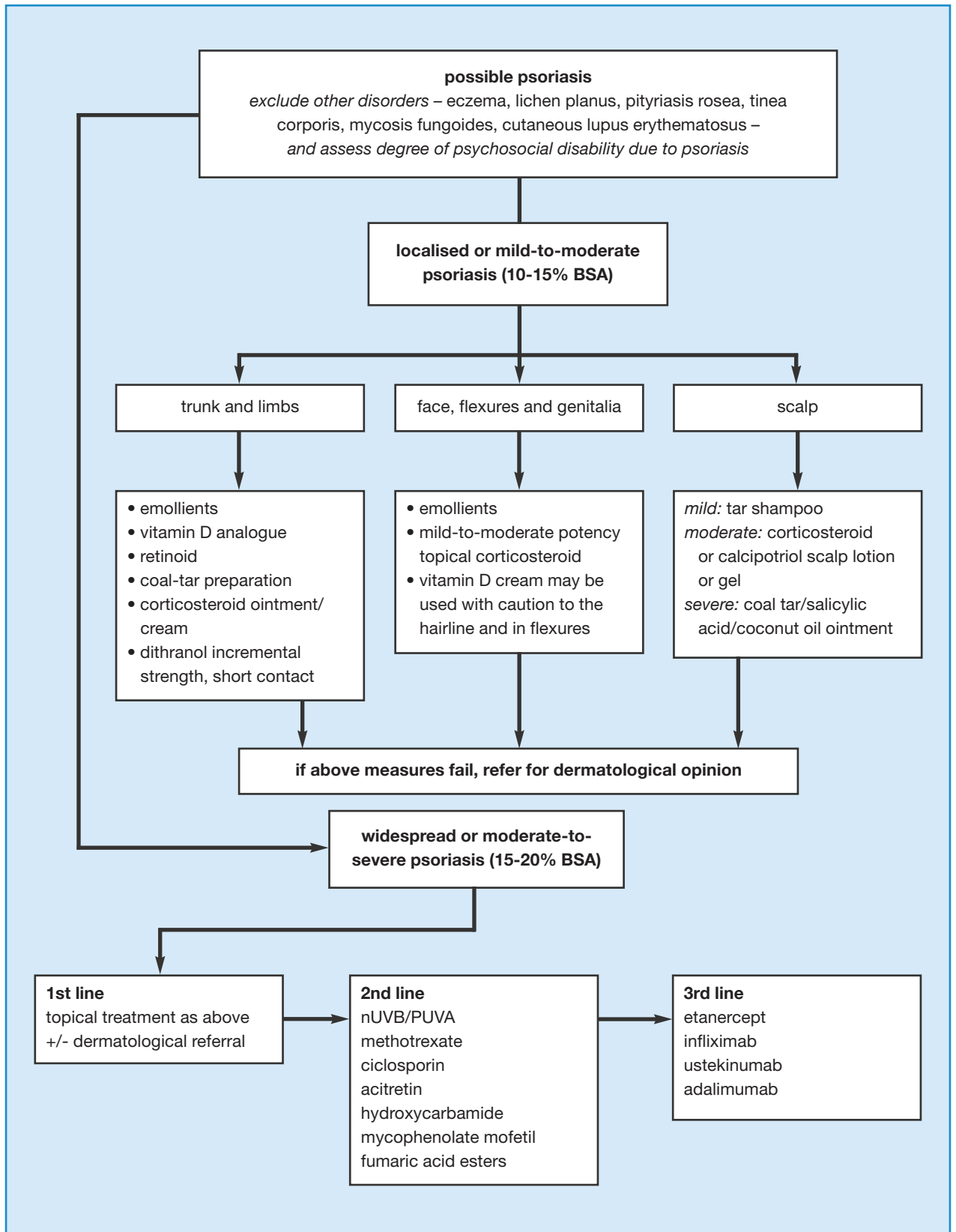


Figure 4. Recommended management of psoriasis (BSA = body surface area)

Key points

- topical treatments (emollients, tar, dithranol, steroids, vitamin D analogues) remain the mainstay of treatment
- preparations combining various topical agents are now available
- narrowband UVB is the first-line phototherapy for psoriasis
- first-line systemic agents for psoriasis include methotrexate and most recently fumaric acid esters, which are being increasingly used; ciclosporin remains an excellent therapeutic option for short-term control of psoriasis where rapid disease response is required
- newer biologic agents have been shown to be effective in psoriasis but long-term safety data are awaited

- Lambert J, *et al. Dermatology* 2002;204:321-4.
- Georgiou S, *et al. Acta Derm Venereol* 1999;79:86.
- Lebwohl MG, *et al. J Am Acad Dermatol* 1998;39:590-6.
- Green C, *et al. Br J Dermatol* 1988;119:691-6.
- Markham T, *et al. Arch Dermatol* 2003;139:325-8.
- Ferguson J. *Arch Dermatol* 1999;135:589-90.
- Stern RS, *et al. J Invest Dermatol* 1988;91:120-4.
- Feldman SR, *et al. J Am Acad Dermatol* 2002;46(6):900-6.

- Roenigk HH Jr, *et al. J Am Acad Dermatol* 1998;38(3):478-85.
- Zachariae H, *et al. Dermatologica* 1987;175(4):178-82.
- Roenigk HH Jr. *J Am Acad Dermatol* 1999;41:S18-21.
- Muller W, *et al. Dtsch Med Wochenschr* 1979;104(29):1047.
- Lowe NJ, *et al. J Am Acad Dermatol* 1996;35:710-9.
- Raman GV, *et al. J Hypertens Suppl* 1998;16:S39-41.
- Smith CH. *Clin Exp Dermatol* 1999;24:2-6.
- Geilen CC, *et al. Br J Dermatol* 2001;144:583-6.
- Altmeyer PJ, *et al. J Am Acad Dermatol* 1994;30(6):977-81.
- Smith CH, *et al. Br J Dermatol* 2009;161:987-1019.
- Gorden KB, *et al. J Am Acad Dermatol* 2006;55:598-606.
- Menter A, *et al. J Am Acad Dermatol* 2008;38:106-15.
- Saurat JH, *et al. Br J Dermatol* 2008;158:556-66.
- NICE. *Infliximab for the treatment of adults with psoriasis*. TA134. January 2008.
- Gottlieb AB, *et al. J Am Acad Dermatol* 2004;53:4-42.
- Reich K, *et al. Lancet* 2005;366:1367-74.
- Leonardi CL, *et al. N Engl J Med* 2003;349:2014-22.
- Papp KA, *et al. Br J Dermatol* 2005;152:1304-12.
- Tyring S, *et al. Lancet* 2006;367:29-35.
- Zachariae C, *et al. Acta Derm Venereol* 2008;88:495-501.
- Krueger GG. *N Engl J Med* 2007;356:580-92.

Dr Higgins is a dermatology registrar and Dr Markham is consultant dermatologist at University Hospital, Galway, Ireland

Resources

Further reading

Psoriasis. Griffiths CEM, *et al.* In: Burns T, *et al.*, eds. *Rook's textbook of dermatology*, 8th ed. Oxford: Wiley-Blackwell, 2010;1589-649.

Guidelines

Adalimumab for the treatment of adults with psoriasis. TA146. NICE, June 2008.

Etanercept and efalizumab for the treatment of adults with psoriasis. TA103. NICE, July 2006.

Infliximab for the treatment of adults with psoriasis. TA134. NICE, January 2008.

Psoriasis – general management. British Association of Dermatologists, 2008. www.bad.org.uk/site/769/Default.aspx.

Psoriasis – management. NHS Clinical Knowledge Summaries. www.cks.nhs.uk/psoriasis.

Ustekinumab for the treatment of adults with moderate to severe psoriasis. TA180. NICE, September 2009.

Groups and organisations

British Association of Dermatologists. Tel: 0207 383 0266; e-mail: admin@bad.org.uk; website: www.bad.org.uk.

Psoriasis Association. Tel: 0845 676 0076; e-mail: mail@psoriasis-association.org.uk; website: www.psoriasis-association.org.uk.

Psoriasis and Psoriatic Arthritis Alliance (PAPAA). Tel: 0870 770 3212; e-mail: info@papaa.org; website: www.paalliance.org.

Websites

www.psoriasis.org. This site is provided by the National Psoriasis Foundation and gives information about psoriasis in general and also current research into psoriasis and treatments.

www.psoriasis-help.org.uk. The Psoriasis Help Organisation site contains information about treatments, and also provides a discussion forum for psoriasis sufferers to exchange views and advice on living with psoriasis.