Phototherapy and systemic treatments

Nick J Reynolds, Simon J Meggitt

A proportion of children and adults with moderate to severe atopic eczema are not adequately controlled with emollients and topical steroids, resulting in significant morbidity and disability. Studies indicate a significant placebo response, so randomized controlled trials of new treatments are vital. This article reviews the evidence for phototherapy and systemic treatments in atopic eczema.

Atopic eczema is very common and a 1-year cross sectional epidemiological study in Lothian, Scotland, reported an overall 1-year prevalence of 2.3% that increased to 9.8% for those aged 2 years and under (Herd et al, 1996). Although the prevalence of atopic eczema declines with age, 38% of the cases in the community were 16 years old and over (Herd et al, 1996). Within the atopic eczema population, there is a large variation in disease severity. For example, global assessment of 1760 children with atopic eczema examined in general practice defined 84% as having mild disease, with only 2% categorized as having severe disease (Emerson et al, 1998). Adults appear more likely to have active disease compared with children (Herd et al, 1996) and adult patients tend to have more severe disease.

The mainstay of treatment for patients with mild to moderate disease remains the appropriate use of emollients and topical steroids. The importance of general measures in the overall management of patients is now widely recognized. These include irritant avoidance, education, demonstration of topical treatments, identification of provoking factors, such as house dust mite and food allergies, and recognition of infection with *Staphylococcus aureus* and herpes simplex. However, there remain a small group of patients with moderate to severe disease whose eczema remains poorly controlled despite optimal first-line measures. The aim of this article is to review the second-line therapeutic options for these patients which now include phototherapy, topical immunomodulatory agents, such as tacrolimus (recently licensed in the UK) and pimecrolimus (not yet available in the UK) and systemic therapy including cyclosporin and azathioprine.

The importance of randomized controlled trials for evaluating treatments for atopic eczema has been stressed (Reynolds, 1997; Hoare et al, 2000) in view of the fluctuating course of the disease and a significant placebo response.

Although the clinical use of phototherapy, topical immunomodulatory therapy, and systemic agents is in many cases backed by good trial data (Hoare et al, 2000), this is not uniformly the case. The use of second-line agents in children heightens concerns about side-effects and for ethical reasons there are fewer published trials in children, although the disease is most prevalent in this age group. In addition, there are few comparative trials of second-line treatments. Therefore, the choice of which second-line therapy to use in patients with moderate to severe disease is largely empirical.

In adult patients with chronic and moderate disease, the authors would usually initiate a trial of phototherapy before considering systemic agents. Factors influencing this decision will include acute *vs* chronic disease, side-effect profile and patient preference. In addition, as the range of second-line therapies for atopic eczema increases, it is likely that physicians will adopt a rotational regimen as has been advocated for systemic therapies in psoriasis (Weinstein and White, 1993). The rationale behind this includes:

1. Some therapies, such as systemic cyclosporin, are licensed only for short courses (8 weeks)
2. Side-effects may be cumulative (Weinstein and White, 1993; Matthews et al, 1996; British Photodermatology Group, 1997)
3. Certain forms of therapy such as narrow-band ultraviolet B (UVB) radiation may induce a period of remission (Reynolds et al, 2001)
4. The agents used have distinct side-effect profiles.

Professor Nick J Reynolds is Professor of Dermatology and **Dr Simon J Meggitt** is Senior Clinical Research Associate, Department of Dermatology, Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH

Correspondence to:
Professor NJ Reynolds
n.j.reynolds@ncl.ac.uk

For patients with an acute exacerbation of atopic eczema, hospital admission to a dermatology ward as a therapeutic manoeuvre should be considered and may relieve the need for second-line systemic therapy.

PHOTOTHERAPY

Patients with atopic eczema often report improvement in summer and following exposure to natural sunlight. This has led to a series of studies that have examined a variety of ultraviolet radiation sources with the aim of determining the most effective therapeutic wavelengths. Studies in Scandinavia, largely conducted on adult patients with relatively mild disease, indicated that ultraviolet A (UVA, 315–400 nm) in addition to UVB (280–315 nm) may improve disease activity.

On the basis of two open uncontrolled studies, a group in Newcastle conducted a randomized controlled trial to compare narrow-band UVB (311 nm), broad-band UVA and visible light (placebo) in adult patients with moderate to severe atopic eczema (Reynolds et al, 2001). This study showed that narrow-band UVB, but not broad-band UVA, is an effective adjunctive treatment and is well tolerated by most patients. Patients were treated twice-weekly for 12 weeks. Sustained improvement 3 months after the end of phototherapy was seen in the narrow-band UVB group. Although narrow-band UVB is widely used in the treatment of psoriasis and is considered to be substantially less carcinogenic than psoralen UVA photochemotherapy (PUVA) (Young, 1995; British Photodermatology Group, 1997), long-term safety of patients receiving appropriate courses of phototherapy will need to be monitored.

For patients with acute severe atopic eczema, high-dose UVA1 (340–400 nm) has been shown, in a randomized controlled trial (Krutmann et al, 1998), to be as effective as moderately potent topical steroids, although special irradiation devices are required which are only available in a few specialist centres.

Photochemotherapy in adults and children

Open studies suggest that PUVA therapy is effective in adults and children (Morison et al, 1978; Sheehan et al, 1993). However, the mean cumulative UVA dose given over a single course was large (1118 J/cm^2) in the study reported by Sheehan et al in 1993, and this induced remission in 80% of children. High temperatures in PUVA cabinets may cause discomfort. Relapse appears more frequent compared with psoriasis. Guidelines published in 1994 recommended PUVA only for patients with severe disease (e.g. for those patients requiring repeated hospital admission) (British Photodermatology Group, 1994). As the carcinogenic potential of narrow-band UVB is considered to be substantially less than that of PUVA (Young, 1995; British Photodermatology Group, 1997), studies of narrow-band UVB in children with atopic eczema are now required to assess efficacy and tolerability.

SYSTEMIC TREATMENTS

Cyclosporin

Systemic cyclosporin inhibits T cell activation by inhibiting the phosphatase calcineurin and preventing nuclear translocation of the transcription factor NFAT. A double-blind, placebo-controlled, crossover study showed that cyclosporin (5 mg/kg/day for 8 weeks) significantly reduced disease activity and area of involvement in adult patients with severe disease (Sowden et al, 1991). These results have been confirmed by further trials. Open trials in children with atopic eczema also report the efficacy of cyclosporin, although continuous rather than intermittent treatment over 1 year appeared to achieve better control (Berth-Jones et al, 1996; Chavanas et al, 2000).

Systemic cyclosporin is now licensed in the UK for short-term use (maximum 8 weeks) in severe refractory atopic eczema in adults and children. The clinical response is rapid but the disease relapses shortly after therapy is stopped. Treatment is in general well tolerated. Kidney function and blood pressure need to be monitored every 2 weeks during therapy and there are concerns about permanent renal impairment and an increased risk of cancer after long-term treatment with cyclosporin (Powles et al, 1998).

TOPICAL IMMUNOMODULATORS

The introduction of this new class of topical drugs in atopic eczema represents an important therapeutic advance. However, it is important to emphasize that comparative studies with systemic agents are required to assess their role in patients with recalcitrant and severe disease. When used systemically tacrolimus inhibits T cell activation by inhibiting calcineurin. The mechanism of action of topical tacrolimus and pimecrolimus remains to be elucidated. Although absorption occurs in only minute quantities, whether these drugs exert systemic immunomodulatory effects through their effects on cells trafficking remains to be determined.

Interestingly, work in the authors' laboratory has shown that human keratinocytes prominently

express the phosphatase, calcineurin and NFAT (Al-Daraji et al, 2002) that are the target of action of cyclosporin, tacrolimus and pimecrolimus in T cells. Further studies are now required to elucidate the relative contribution of calcineurin inhibition in T cells, keratinocytes, mast cells and antigen-presenting cells to the therapeutic action of topical immunomodulators in atopic eczema.

Azathioprine

Although azathioprine is not licensed for use in atopic eczema in the UK, a survey has shown that 75% of UK consultant dermatologists use azathioprine to treat patients with severe disease that is resistant to conventional topical treatment (Tan et al, 1997). There are several small, uncontrolled studies that suggest azathioprine may be effective (Meggitt and Reynolds, 2001).

The need for a randomized controlled trial has, however, only recently been recognized (Meggitt and Reynolds, 2001; Graham-Brown et al, 2002) and the results of one randomized crossover study have just been published (Graham-Brown et al, 2002). A retrospective study suggests that azathioprine may also be effective in children with severe atopic eczema (Murphy and Atherton, 2002) and an excellent or good response was observed in 38 out of 48 children. The drug was well tolerated apart from reversible abnormalities in liver function tests.

Side-effects from azathioprine used as monotherapy are not insignificant and include hypersensitivity reactions, gastrointestinal upset, myelotoxicity and hepatotoxicity. The differential susceptibility of patients to azathioprine-induced myelosuppression relates to the activity of a key enzyme, thiopurinemethyltransferase (TPMT), in azathioprine metabolism. Patients who are homozygous for the $TPMT^{L}$ allele ($TPMT^{LL}$) have undetectable TPMT enzyme activity and are at significant risk of developing profound myelosuppression. The frequency of these individuals in Caucasian populations is approximately 1 in 300. Approximately 10% of the population in Western countries are heterozygous ($TPMT^{LH}$) at the TPMT locus and are at intermediate risk of myelotoxicity. It is now recommended that TPMT status is checked by measuring erythrocyte TPMT activity before initiation of azathioprine therapy for dermatological disease (Meggitt and Reynolds, 2001).

The authors recently conducted an open pilot study in adult patients using a dosage regimen based on baseline TPMT activity. This formed the basis for an ongoing randomized controlled trial. A 25% reduction in disease activity score was observed in an open study over a mean duration of treatment of 11 weeks, with sustained improvement at 3 months after stopping therapy in seven out of 12 patients. Two patients developed reversible hepatotoxicity (Meggitt and Reynolds, 2001).

SYSTEMIC STEROIDS

Systemic steroids are effective in controlling atopic eczema although relapse is often rapid after steroid therapy is tapered and then stopped. However, prolonged use is associated with predictable and serious toxicity (e.g. osteoporosis). Therefore the authors use short courses only very rarely.

Mycophenolate mofetil

Mycophenolate mofetil is broken down to the active metabolite mycophenolic acid which blocks the proliferative responses of T and B lymphocytes. This immunosuppressive agent has been used in a variety of inflammatory and immunobullous skin diseases. In an open trial, Neuber et al (2000) described a 68% median reduction in disease-activity score in 10 adult patients with atopic eczema. Interestingly, this was accompanied by significant reduction in immunoglobulin (Ig) E and a concomitant increase in gamma-interferon. The initial dose was 1 g daily for 1 week increasing to 2 g daily for a further 11 weeks. Monitoring for myelosuppression and liver function test abnormalities are required, although no toxicity was observed in this study. Further placebo-controlled and comparative studies are required to evaluate its place in therapy.

SPECIFIC IMMUNOMODULATORY THERAPIES

Gamma-interferon therapy and thymopentin

Because atopic dermatitis is associated with a skew towards a Th_2 T helper cell phenotype, low gamma-interferon production and high serum levels of IgE, therapeutic trials of recombinant gamma-interferon therapy have been performed.

Clinical benefit has been observed in two randomized controlled studies. The first, published in 1993, involved subcutaneous recombinant gamma-interferon given daily for 12 weeks and resulted in 50% improvement in physicians' global scores at the end of the treatment phase compared with 21% of patients receiving placebo (Hanifin et al, 1993). Interestingly, however, no reduction in serum IgE was observed. A second study, published in 2000, also reported significant improvement in clinical scores compared with placebo when treatment with recom-

binant gamma-interferon was given three-times weekly for 12 weeks (Jang et al, 2000). Flu-like symptoms and mild elevation of liver transaminase were reported in both studies. The efficacy of gamma-interferon therapy appeared to be maintained in a 22-month open study involving 15 adult and paediatric patients, and no long-term safety issues were identified (Schneider et al, 1998). However, gamma-interferon therapy is not licensed for treatment of atopic eczema in the UK and the mode of delivery and side-effect profile mean that this form of therapy should still be regarded as experimental.

The thymic hormone thymopentin regulates the differentiation of thymocytes and the function of mature T cells. Thymopentin is a synthetic immunomodulatory pentapeptide, comprising amino acids 32–36 of the parent thymopoitein, that retains biological and pharmacological activities of the parent compound. Double-blind, placebo-controlled trials of subcutaneous thymopentin administered daily or three-times weekly showed a reduction in specific clinical score parameters, although the absolute changes compared with placebo appeared relatively small (Leung et al, 1990; Stiller et al, 1994). Side-effects appeared limited, but the development of this drug or its derivative does not appear to have been pursued.

CHINESE HERBAL MEDICINE

Clinical observation of improvement in patients receiving Chinese herbal medicine led to a double-blind, placebo-controlled, trial in 40 patients using a standardized tea preparation during 8 weeks of treatment (Sheehan et al, 1992). The preparation was unpalatable, however, and there have been concerns over renal and hepatotoxicity (Harper, 1994). Studies are currently under way to try and identify the active ingredient and improve its safety profile.

KEY POINTS

- Narrow-band ultraviolet B phototherapy is an effective adjunctive treatment for moderate to severe atopic eczema and may lead to a period of remission.
- Cyclosporin is an effective systemic treatment for severe atopic eczema but is currently recommended only for short-term use.
- The concept of rotational second-line therapy should be considered for atopic eczema.
- There is a need for comparative studies of second-line agents, including topical immunomodulators.
- The value of hospital admission for acute severe flares should not be underestimated and may avoid the necessity for second-line agents.

CONCLUSIONS

The beneficial effects of phototherapy and the short-term use of systemic agents have now been established in the management of severe atopic eczema. In addition, it is likely that the topical immunomodulators – tacrolimus and pimecrolimus – will have an important role in the management of moderate to severe disease. However, comparative studies of these treatments remain a priority. In view of the differing side-effect profiles of second-line agents, the concept of rotational therapy provides the best opportunity to optimize patient management and minimize long-term toxicity of these drugs.

Novel treatments based on increased knowledge of the immunopathogenesis of atopic eczema remain experimental, and may be limited in practicality by their mode of administration. The association of variants within Th_2 cytokine receptor genes (Hershey et al, 1997) and the linkage of specific loci to atopic eczema (Lee et al, 2000; Cookson et al, 2001) should, over the next decade, lead to identification of predisposing genes and increased understanding of disease pathogenesis. This should result in important therapeutic advances. HM

Professor Reynolds and Dr Meggitt are currently supported by research grants from the Wellcome Trust. NJR is a recipient of a Wellcome Research Leave Award for Clinical Academics.
Conflict of interest: Professor Reynolds, through the University of Newcastle upon Tyne, is a member of an advisory panel to Fujisawa. The University and Professor Reynolds' department has received income from this.

Al-Daraji W, Grant KR, Saxton A, Ryan K, Reynolds NJ (2002) Localization of calcineurin/NFAT in human skin and psoriasis and inhibition of calcineurin/NFAT activation in human keratinocytes by cyclosporin A. *J Invest Dermatol* **118:** 779–88
Berth-Jones J, Finlay AY, Zaki I et al (1996) Cyclosporine in severe childhood atopic dermatitis: a multicenter study. *J Am Acad Dermatol* **34:** 1016–21
British Photodermatology Group (1994) British Photodermatology Group guidelines for PUVA. *Br J Dermatol* **130:** 246–55
British Photodermatology Group (1997) An appraisal of narrowband (TL-01) UVB phototherapy. British Photodermatology Group Workshop Report (April 1996). *Br J Dermatol* **137:** 327–30
Chavanas S, Bodemer C, Rochat A et al (2000) Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet* **25:** 141–2
Cookson WO, Ubhi B, Lawrence R et al (2001) Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. *Nat Genet* **27:** 372–3
Emerson RM, Williams HC, Allen BR (1998) Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *Br J Dermatol* **139:** 73–6
Graham-Brown RA, Takwale A, Tan E et al (2002) Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *Br J Dermatol* **147:** 342–30
Hanifin JM, Schneider LC, Leung DY et al (1993) Recombinant interferon gamma therapy for atopic dermatitis. *J Am Acad Dermatol* **28:** 189–97
Harper J (1994) Traditional Chinese medicine for eczema. *Br Med J* **308:** 489–90
Herd RM, Tidman MJ, Prescott RJ, Hunter JA (1996) Prevalence of atopic eczema in the community: the Lothian Atopic Dermatitis study. *Br J Dermatol* **135:** 18–19

Hershey GK, Friedrich MF, Esswein LA, Thomas ML, Chatila TA (1997) The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. *N Engl J Med* **337:** 1720–5

Hoare C, Li Wan Po A, Williams H (2000) Systematic review of treatments for atopic eczema. *Health Technol Assess* **4**(37): 1–191

Jang IG, Yang JK, Lee HJ et al (2000) Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. *J Am Acad Dermatol* **42:** 1033–40

Krutmann J, Diepgen TL, Luger TA et al (1998) High-dose UVA1 therapy for atopic dermatitis: results of a multicenter trial. *J Am Acad Dermatol* **38:** 589–93

Lee YA, Wahn U, Kehrt R et al (2000) A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. *Nat Genet* **26:** 470–3

Leung DY, Hirsch RL, Schneider L et al (1990) Thymopentin therapy reduces the clinical severity of atopic dermatitis. *J Allergy Clin Immunol* **85:** 927–33

Matthews D, Fry L, Powles A et al (1996) Evidence that a locus for familial psoriasis maps to chromosome 4q. *Nat Genet* **14:** 231–3

Meggitt SJ, Reynolds NJ (2001) Azathioprine for atopic dermatitis. *Clin Exp Dermatol* **26:** 369–75

Morison WL, Parrish J, Fitzpatrick TB (1978) Oral psoralen photochemotherapy of atopic eczema. *Br J Dermatol* **98:** 25–30

Murphy LA, Atherton D (2002) A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* **147**(2): 308–15

Neuber K, Schwartz I, Itschert G, Dieck AT (2000) Treatment of atopic eczema with oral mycophenolate mofetil. *Br J Dermatol* **143:** 385–91

Powles AV, Hardman CM, Porter WM, Cook T, Hulme B, Fry L (1998) Renal function after 10 years' treatment with cyclosporin for psoriasis. *Br J Dermatol* **138:** 443–9

Reynolds NJ (1997) Recent advances in atopic dermatitis. *J R Coll Physicians Lond* **31**(3): 241–5

Reynolds NJ, Franklin V, Gray JC, Diffey BL, Farr PM (2001) Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. *Lancet* **357:** 2012–6

Schneider LC, Baz Z, Zarcone C, Zurakowski D (1998) Long-term therapy with recombinant interferon-gamma (rIFN-gamma) for atopic dermatitis. *Ann Allergy Asthma Immunol* **80:** 263–8

Sheehan MP, Atherton DJ, Norris P, Hawk J (1993) Oral psoralen photochemotherapy in severe childhood atopic eczema: an update. *Br J Dermatol* **129:** 431–6

Sheehan MP, Rustin MH, Atherton DJ et al (1992) Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet* **340:** 13–17

Sowden JM, Berth-Jones J, Ross JS et al (1991) Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet* **338:** 137–40

Stiller MJ, Shupack JL, Kenny C, Jondreau L, Cohen DE, Soter NA (1994) A double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of thymopentin as an adjunctive treatment in atopic dermatitis. *J Am Acad Dermatol* **30:** 597–602

Tan BB, Lear JT, Gawkrodger DJ, English JS (1997) Azathioprine in dermatology: a survey of current practice in the UK. *Br J Dermatol* **136**(3): 351–5

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

Young AR (1995) Carcinogenicity of UVB phototherapy assessed. *Lancet* **345:** 1431–2