Tacrolimus ointment for the management of atopic dermatitis

Malcolm Rustin

The management of atopic dermatitis is set for a major shift with the introduction of the first new topical treatment for the condition in 40 years – the non-steroidal topical immunomodulator tacrolimus (Protopic®). Backed by strong clinical data, tacrolimus ointment is a valuable addition to topical steroids in the management of moderate-to-severe atopic dermatitis.

Atopic dermatitis (AD; eczema) is the commonest inflammatory skin condition. Its prevalence has tripled in the last 30 years and it affects 15–20% of children and approximately 4% of adults. Data on the likelihood of children continuing to suffer from atopic eczema are poor. An often quoted figure is that 90% of childhood eczema clears by puberty (Vickers, 1980), but this is probably over-optimistic. Only 60% of children have overall clearance with 40% suffering either episodic or sustained disease (Graham-Brown, 2001).

The main features of atopic eczema are dry skin and intense itchiness. The condition tends to occur in patches, which can flare up at intervals, becoming blistered and oozing. These can affect any part of the body, although the face, neck, insides of the elbows and behind the knees are most commonly affected. In many patients, the skin becomes raw from scratching and can easily become infected.

Involved skin is invariably colonized with *Staphylococcus aureus* and there is evidence that this infection aggravates the eczema. This is thought to occur by the secretion of exotoxins which act as superantigens resulting in direct proliferation and activation of T lymphocytes (Bunikowski et al, 1999). Application of superantigens to the normal skin of patients with atopic eczema can induce eczema and superantigens can also augment synthesis of allergen-specific immunoglobulin E (Hofer et al, 1999) and induce glucocorticoid resistance (Hauk et al, 2000). Atopic eczema generally follows a chronically relapsing course. There may be periods with no symptoms, followed by 'flares', with eruptions of scaling, crusting and irritation, which may last for several weeks or months.

The cause of atopic eczema is unknown, although a genetic predisposition and a combination of allergic and non-allergic factors appears to be important in determining disease expression (Hoare et al, 2000).

There is a close association between atopic eczema and allergy: 60–70% of patients with atopic eczema have a personal or family history of atopic disease, including asthma, hay fever or allergies. Research suggests that atopic eczema is an allergic disorder, with many similarities to asthma (Leung and Soter, 2001), which appears to have a strong environmental component. A worldwide study showed wide variations in the prevalence of atopic eczema both within and between different countries inhabited by similar ethnic groups, suggesting that environmental factors may be critical in determining disease expression (Robertson et al, 1999). Potential suspects include high house dust mite levels in modern centrally heated homes, greater exposure to air pollution, smaller families with less exposure to infections, more pets, higher maternal age and a wider range of foods (Barnetson and Rogers, 2002).

Atopic eczema is sometimes dismissed as a minor skin condition, but moderate-to-severe atopic eczema can have a profound effect on the quality of life, both for sufferers and their families. Patients generally suffer intractable itching, skin damage, skin soreness, sleep loss and the social stigma of having a visible skin disease. They often need to apply topical agents on a daily basis (Hoare et al, 2000). Many patients scratch their skin until it bleeds, and some remove the top layer of skin, increasing the risk of infection.

An unpublished survey in 2001 by the National Eczema Society of 455 people with the condition revealed that nearly nine in every ten (88%) considered that at least one aspect of their lives was adversely affected, including self-confidence, ability to socialize and even career choice.

Dr Malcolm Rustin is Consultant Dermatologist in the Department of Dermatology, Royal Free Hospital, London NW3 2QG

TREATING ATOPIC DERMATITIS

AD has traditionally been treated with emollients, topical steroids and antibiotics if secondarily infected. The aim is to control symptoms and disease, as cure is not possible. Less widely used options include coal tar, systemic corticosteroids, phototherapy, traditional Chinese herbal therapy (Sheehan et al, 1992) and systemic immune response modifiers including azathioprine (Berth-Jones et al, 2002), cyclosporin (Berth-Jones et al, 1997) and high-dose intravenous immunoglobulin. There is little good evidence – based on randomized, controlled trials – for many treatments used in AD, including some commonly used treatments, e.g. combinations of topical antibiotics and corticosteroids (Hoare et al, 2000).

Topical steroids have been the mainstay of AD treatment since 1952. Subsequent modifications of molecules and formulations have led to a range of different agents with different potencies. Mild-to-moderately potent topical steroids can be very effective in clearing up small patches of eczema but their side effects are problematic. More potent steroids produce side effects such as rosacea and skin atrophy, which can lead to striae and steroid telangiectasia. Less often, topical steroids cause hypopigmentation, secondary infection and acne (Boguniewicz and Leung, 1996a). The atrophogenicity of topical steroids limits their use on thin skin, e.g. the face, neck and flexure regions, and some patients become resistant to them, limiting their long-term use (Reitamo et al, 1998). Growth retardation has been associated with long-term use of mid- to high-potency corticosteroids in children (Boguniewicz and Leung, 1996b).

TACROLIMUS OINTMENT

Tacrolimus is a macrolide that was originally isolated from the fungus *Streptomyces tsukubaensis*. Tacrolimus inhibits T lymphocytes which release cytokines triggering the inflammation which underlies AD. Tacrolimus also affects other cells including Langerhans and mast cells. In contrast, steroids are much broader spectrum immunosuppressants. By downregulating T cells, the symptoms of AD – such as intense itchiness and dry, swollen, blistered and oozing skin – begin to fade within a few days of using tacrolimus ointment.

Topically applied tacrolimus penetrates the skin sufficiently to allow local immunomodulation but the skin does not act as a reservoir for this drug and very little tacrolimus passes through the dermis into the circulation (Ruzicka et al, 1997). Systemic levels of tacrolimus are low in patients treated topically with it and fall over time – indicating that the absorption of tacrolimus into the bloodstream decreases as the skin heals, with no absorption through the skin of healthy controls (Kawashima et al, 1996).

EFFICACY OF TACROLIMUS OINTMENT

Trials have been carried out in over 17 000 patients with tacrolimus ointment, showing good efficacy and tolerability. Key studies in the development of tacrolimus ointment include short- and long-term trials – a 3-week adult trial, two 12-week adult trials, one 12-week paediatric study and 1-year studies in adults and children. An early phase III trial with tacrolimus ointment showed clear efficacy in patients with moderate-to-severe AD. After 3 weeks of treatment, the median percentage decrease in the summary score for dermatitis on the trunk and extremities was 67% for patients treated with 0.03% tacrolimus ointment and 83% for those treated with 0.1% tacrolimus ointment, compared to only 22.5% for patients receiving vehicle alone ($P<0.001$). Results were similar for the face and neck (Ruzicka et al, 1997).

More recent trials have shown maintained efficacy and safety when tacrolimus ointment is used for at least a year. A study of 255 children aged 2–15 years, with moderate-to-severe AD, showed that 0.1% tacrolimus ointment applied twice daily for up to 12 months achieved long-term efficacy and safety. Results showed substantial improvements in signs and symptoms of AD, per cent body surface area affected and pruritus. Improvement in all efficacy variables was seen after 1 week of therapy, improvement was maintained and most patients continued to improve during the remaining 12 months of the study. There was no increase in incidence of infections or other significant adverse events (Kang et al, 2001).

A 1-year, single arm study in adults showed an increasing percentage of patients showing marked improvement or clearance over time – 54% at 1 week, 81% at 6 months and 86% at 1 year. Patients applied 0.1% tacrolimus ointment until 7 days after cessation of itch and then restarted based on the presence of itch. There was no rebound effect – sometimes seen after topical steroid withdrawal – after tacrolimus ointment therapy was stopped (Reitamo et al, 2000).

One- and 3-year long-term studies in adults have shown sustained benefit with no increase in skin infections, no reduction in immunocompetence and minimal systemic absorption (Reitamo et al, 2000; Caro et al, 2002).

TACROLIMUS OINTMENT *VS* TOPICAL CORTICOSTEROIDS

Comparative trials with tacrolimus ointment have shown equivalence to potent topical corticosteroids (Nakagawa et al, 1998). A large, phase III,

parallel-group study compared 0.03% and 0.1% tacrolimus ointment with topical steroid 0.1% hydrocortisone butyrate ointment in 570 adult patients with moderate-to-severe AD. The efficacy of 0.1% tacrolimus ointment was similar to the corticosteroid (Reitamo et al, 2002a). Tacrolimus showed similar eczema clearance (defined as more than 75% clearance) in a trial comparing it to the same topical corticosteroid with both treatments achieving clearance in 60–80% of patients over 3 weeks (*Figure 1*). In children, tacrolimus ointment achieved greater eczema clearance than the mild topical steroid hydrocortisone acetate (Reitamo et al, 2002b) (*Table 1*).

TOLERABILITY OF TACROLIMUS OINTMENT

The commonest side effect of tacrolimus ointment is a mild-to-moderate burning and stinging sensation. However, this usually occurs only during the first few days of treatment and lasts 15–20 minutes. It is important to warn patients about these symptoms in advance, and reassure them that they should soon disappear. Tacrolimus ointment does not cause skin thinning so can be used on the face and neck – areas of the body that have had to be avoided with steroids. A randomized, placebo-controlled trial in patients with AD and healthy volunteers showed no reduction in skin thickness – assessed by ultrasound – with tacrolimus ointment, while betamethasone reduced skin thickness by a median of 7–8% (Reitamo et al, 1998).

One-year studies with tacrolimus ointment have revealed no safety issues. The incidence of skin infections was similar to that seen overall in the AD population and were less common than before treatment started. Systemic absorption of tacrolimus ointment was minimal, so any systemic immunosuppression seems unlikely (Allen, 2002).

Tacrolimus ointment (Protopic® 0.03% and 0.1%, Fujisawa Limited, Staines) has been licensed for adults with moderate-to-severe AD who are not adequately responsive to, or are intolerant of conventional therapies. Protopic 0.03% can also be used in children (aged 2 years and above) who are not responsive to conventional therapies. The ointment should be used together with emollients but they should not be applied in the same area within 2 hours.

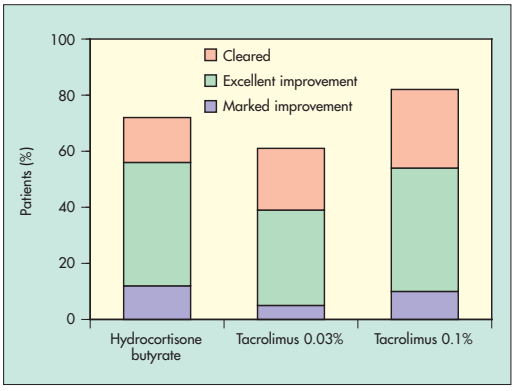

Figure 1. Physicians' evaluation of clinical response to treatment at week three. From Reitamo et al (2002a).

TABLE 1.
Treatment of atopic eczema with corticosteroids *vs* tacrolimus ointment

Topical corticosteroids	Skin thinning
	Moderately improves itching
	Tachyphylaxis may develop over time
	Poor long-term control possibly as a result of topical corticosteroid phobia
Tacrolimus ointment	No skin thinning*
	Markedly improves itching
	No tachyphylaxis over time
	Good long-term control
	Rapid onset of action, improvement seen as early as after 3 days of treatment†

*Reitamo et al (1998); † Ruzicka et al (1999)

TACROLIMUS IN CLINICAL PRACTICE

Tacrolimus ointment is available in two strengths – 0.03% and 0.1%. The strength used depends on the severity of AD and the patient's age. In adults, the dose indicated is 0.1% twice daily for the first 3 weeks, stepping down to 0.03% twice daily once the skin has improved. In children, the dose indicated is 0.03% twice daily for the first 3 weeks, then once daily until clearance has been achieved. Patients should be advised to spread a thin layer on affected areas – a pea-sized amount of ointment should cover a 2-inch diameter area of skin. Skin should be completely dry before applying the ointment and dressings should not be used on affected areas. Emollients should be used while using tacrolimus ointment but should not be applied in the same area within 2 hours (Fujisawa, unpublished data, 2002).

If topical tacrolimus is equivalent to a potent topical steroid, how should it be used – as monotherapy instead of topical steroids, or only when topical steroids fail? The product licence advises that it should be used in patients with moderate-to-severe disease who have failed to respond adequately to conventional therapy. Until now, it has been difficult to know what to do in a patient where mild-to-moderately potent steroids were no longer effective or the eczema had become too severe to deal with. Use of more potent steroids has been problematic because of the risk of serious side effects. Patients are generally very reluctant to use strong steroids, making compliance a problem. Tacrolimus ointment offers

a major advance because it is free from the side effects that have dogged the use of topical steroids.

Tacrolimus ointment provides a useful new option in patients who have used topical steroids for 2 weeks and gained no benefit. Tacrolimus ointment is likely to be particularly useful for eczema on the face and neck, where prolonged use of topical steroids more potent than 1% hydrocortisone is inappropriate. There has not previously been an effective long-term treatment for facial eczema that was suitable for use in general practice – tacrolimus ointment offers a viable option without the risk of glaucoma. It is also likely to be useful in patients with very widespread disease, including the face and around the eyes.

Although tacrolimus ointment is more expensive than topical steroids, its use is likely to prove cost-effective if this avoids the need for systemic treatments and possibly hospital referrals. Figures on the costs of treating AD suggest that patients spend an average of £25.90 every 2 months on treating their condition, while the cost of this treatment to the NHS is £16.20 (Herd et al, 1996). If these figures were extrapolated to the UK population, the annual cost to patients with atopic eczema would be £297 million per year, and the cost to the NHS would be £125 million each year. Atopic eczema costs an estimated £43 million each year in lost working days (Herd et al, 1996).

CONCLUSION

Tacrolimus ointment is a welcome addition to the range of therapies available for the treatment of moderate-to-severe AD. There is good evidence for its efficacy and tolerability. Short- and long-term trials have shown clear benefit and good tolerability. Tacrolimus ointment offers an important new option for physicians and their patients suffering from AD. It introduces the potential for long-term, intermittent monotherapy for the treatment of moderate-to-severe AD. HM

Conflict of interest: Dr Rustin has acted as a consultant for Fujisawa Ltd, participated in clinical trials for tacrolimus ointment in atopic eczema and is undertaking research into the mode of action of tacrolimus ointment in the treatment of atopic eczema.

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KEY POINTS

- Protopic (tacrolimus ointment) can be used for adults with moderate-to-severe atopic eczema who are not adequately responsive to or are intolerant of conventional therapies.
- Protopic 0.03% can be used for children (2 years of age and above) with moderate-to-severe atopic eczema who fail to respond adequately to conventional therapies.
- Protopic 0.1% and 0.03% is a real alternative for treatment challenges associated with topical corticosteroids.
- Protopic offers safe and effective long-term disease management in adults and children.
- It is the treatment of choice for sensitive skin regions.