

## Atopic eczema in primary care



### SUMMARY

This *Bulletin* looks at the management of atopic eczema in primary care. It reviews the new topical products, tacrolimus (*Protopic*<sup>®</sup>) and pimecrolimus (*Elidel*<sup>®</sup>), but other specialist treatments (e.g. phototherapy and oral immunosuppressants) are not covered.

- Despite a lack of good quality randomised controlled trials, emollients are important in the management of atopic eczema and they should be used regularly by all patients.
- When used intermittently to control exacerbations, topical corticosteroids are effective and patients should be reassured that side effects are rarely seen in primary care.
- Moderate to severe infection should be managed with oral antibiotics. Topical antibiotics with or without corticosteroids have little place in therapy.
- Defining the role of the new topical products, tacrolimus and pimecrolimus, is difficult. Trial data are limited and their long-term safety is unknown. However, at the current time, it seems sensible to recommend against general use of pimecrolimus, and to recommend that treatment with tacrolimus should be initiated and supervised by a specialist.

### Introduction

Atopic eczema or atopic dermatitis, as it is more frequently called in the USA, is a common chronic inflammatory skin condition, affecting 15–20% of schoolchildren and 2–10% of adults.<sup>1,2</sup> In the majority of patients it begins in early childhood, often in the first year of life, when it can be particularly severe. Although about 60% of children outgrow the disease or experience milder symptoms as they get older, the tendency towards dry and irritable skin is probably lifelong, and the condition can recur in adults, often as hand eczema.<sup>2–5</sup>

The precise cause of atopic eczema is unknown but immunological, genetic and environmental factors play a role.<sup>5</sup> Atopic eczema is strongly associated with other atopic diseases, such as asthma and hay fever, all of which have increased in prevalence over the past 30 years.<sup>4,5</sup>

### How is atopic eczema diagnosed?

Atopic eczema is likely if the patient has an itchy skin condition plus three or more of:<sup>1,5</sup>

- A history of itching of the skin creases, e.g. bends of elbows or behind knees (or cheeks in young children)
- A personal or immediate family history of asthma or hay fever
- A tendency towards dry skin
- Flexural eczema or eczema affecting the cheeks, forehead or outer limbs in young children (visible or from history)
- Onset under the age of two years.

When patients present, it is important to take a comprehensive personal and family history of atopy and eczema, including a discussion of possible exacerbating factors. A full skin examination is also necessary to note the extent, location and severity of the condition.<sup>1,5</sup> Infective complications are common, and bacterial infection with *Staphylococcus aureus* may manifest as typical bullous impetigo or as a worsening of the eczema with increased redness, oozing and crusting. Herpes simplex infection, indicated by grouped vesicles and punched out erosions, can also occur.<sup>1,3</sup> If a severe, widespread herpes simplex infection (eczema herpeticum) is suspected, immediate referral to secondary care is required for prompt antiviral treatment.<sup>1,6</sup>

### How should atopic eczema be managed?

Most patients with atopic eczema can be managed in primary care using a multipronged approach, which involves the identification and avoidance of exacerbating factors, skin care and anti-inflammatory treatment.<sup>4</sup> Referral to a specialist is advised if the condition is severe and has not responded to appropriate therapy.<sup>1,6</sup>

Unfortunately, the evidence base for prevention and treatment of atopic eczema is poor. A recent systematic review conducted for the Health Technology Assessment Programme concluded that most of the evidence came from poorly reported, short-term trials of 'me-too' products, which lacked common outcome measures that are important to both patients and doctors.<sup>2</sup> Because of this, eczema

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management guidelines, such as those produced by the Primary Care Dermatology Society and the British Association of Dermatologists (**Panel 1**),<sup>1</sup> whilst useful, tend to be consensus-based.

### Avoiding exacerbating factors

Where practical, factors that exacerbate eczema, such as extremes of temperature or irritants should be avoided.<sup>1</sup> Irritants include clothes containing wool or certain synthetic fibres, and soaps or detergents (which should be replaced with emollients). Airborne allergens — in particular house dust mite — can also be exacerbating factors. However, avoiding these can be difficult, time consuming and costly, and may only be of limited benefit.<sup>1,7</sup> Likewise, although foods such as eggs, cow's milk, peanuts or tartrazine can be aggravating factors, true food allergy probably occurs in fewer than 10% of children with atopic eczema, and only those foods that clearly cause exacerbations should be avoided, with dietetic advice.<sup>1,3</sup>

### Using emollients

Despite a lack of good quality randomised controlled trials (RCTs), emollients are a well-established, first-line therapy for atopic eczema.<sup>1,2,5</sup> Most patients with eczema have dry skin and the aim of using emollients is to retain the skin's barrier function (keeping water in and irritants or pathogens out) and to prevent painful cracking.<sup>2</sup>

The use of emollients in dry skin conditions was discussed in a previous *MeReC Bulletin* (Vol 9, No 12 — see NPC website). In summary, it is important that patients use emollients (e.g. bath oils, soap substitutes and moisturisers) frequently and continuously. Therefore, patient acceptability, as well as cost, is important when choosing products. Generally, the greasier the

preparation, the better the emollient effect, but very greasy ointments may not be acceptable to patients.<sup>5</sup>

Emollients are best applied when the skin is moist, e.g. during (as soap substitutes) and immediately following a lukewarm bath, but they can and should be applied at other times. Application every four hours or at least three to four times a day is recommended<sup>1</sup> but this may not be practical, and regular use just once a day may be an improvement for many patients. If a large part of the body is affected, quantities in the order of 250g per week for children and 500g per week for adults may be required.<sup>5</sup>

### How should topical corticosteroids be used?

Topical corticosteroids have been used for atopic eczema for about 40 years, and their effectiveness is supported by reasonable RCT evidence.<sup>2</sup> Despite popular misconceptions, when topical corticosteroids are used appropriately side effects, such as skin thinning, are rarely seen in primary care, and patients should be reassured about this (**Panel 2**).<sup>2</sup> A previous *MeReC Bulletin* (Vol 10, No 6 — see NPC website) discussed the safety of topical corticosteroids in more detail. It also looked at practical issues, such as the number of finger tip units of ointment or cream required to cover different areas of the body adequately.

In general, topical corticosteroids should only be used intermittently to control exacerbations. A 'step-up' approach, from less potent to more potent topical corticosteroids, or a 'step-down' approach from more potent to less potent preparations is often recommended.<sup>1</sup> However, there is no convincing evidence that either is better than simple 'start-stop' bursts of a suitably potent preparation.<sup>8</sup> In a RCT of 174 children with mild or moderate atopic eczema, a short burst of a potent topical corticosteroid (betamethasone valerate 0.1% for three days) was as effective as seven days' treatment with hydrocortisone acetate 1% at controlling flares.<sup>9</sup>

Recently, a RCT in 295 adults with atopic eczema found that twice-weekly maintenance treatment with a potent topical corticosteroid (fluticasone propionate) in addition to emollients reduced the risk of relapse.<sup>10</sup> However, generalising these findings to primary care is difficult, as patients were recruited from dermatology outpatient clinics and had moderate to severe disease.

Older topical corticosteroids, such as hydrocortisone or betamethasone, are conventionally applied twice daily, giving a perception that the newer, more expensive, once-daily preparations, such as fluticasone propionate, are advantageous.<sup>8</sup> However, there is no clear evidence to support twice-daily over once-daily use of any topical corticosteroid,<sup>2</sup> and using older, cheaper preparations once a day as a first choice in all patients with atopic

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#### Panel 1: General principles of managing atopic eczema in primary care<sup>1</sup>

- Keep the patient/parent informed
  - explain the condition and its treatment
  - educate the patient on the use of topical treatments, including details of application and quantities. Ideally, demonstrate how and when to use them (involve practice nurses)
  - back this up with written information and practical advice, see the British Association of Dermatologists website ([www.bad.org.uk](http://www.bad.org.uk)) and the National Eczema Society website ([www.eczema.org](http://www.eczema.org))
- Advise the patient to avoid exacerbating factors, where practical, such as extremes of temperature and irritants
- Advise the patient to keep nails short and avoid scratching
- Advise the patient on how to keep the skin hydrated
  - use of baths and bath additives
  - liberal use of emollients, ideally when skin is moist
- Treat exacerbations
  - use of appropriate topical corticosteroids on an acute basis
- Treat secondary infection early
  - use of appropriate topical (but see text) and oral antibiotic therapy

eczema seems sensible. The National Institute for Clinical Excellence (NICE) appraisal of topical corticosteroids for atopic eczema is expected in July 2004.

For severe atopic eczema, there is limited evidence from small studies in children (most of which were not RCTs) that using topical corticosteroids under 'wet wraps' is effective.<sup>7</sup> However, there is a higher risk of side effects when topical corticosteroids are occluded, and 'wet wrapping' should only be initiated by specialists and supervised by appropriately trained health care professionals.<sup>8,11</sup>

### What about managing bacterial infection?

The skin of most patients with atopic eczema is colonised with *Staphylococcus aureus*, but the role that this pathogen plays in the condition is unclear.<sup>1,2</sup> For patients with clinical signs of moderate to severe infection, such as sore pus spots, oral antibiotics are indicated. A seven-day course of flucloxacillin or erythromycin is recommended first line.<sup>12</sup> However, for patients with non-clinically infected eczema or borderline infection (i.e. just redness and oozing), management is less clear.<sup>2</sup>

Concerns over resistance, and a lack of evidence for efficacy, argue against widespread, routine use of antibiotics and antimicrobials. There is no evidence that topical antibiotic/corticosteroid preparations are superior to corticosteroids alone,<sup>2,7</sup> and topical antibiotics should be avoided or reserved for single small lesions only.<sup>12</sup> Likewise, there is no evidence that bath oils containing antimicrobials are any more effective than standard bath oils and their routine use cannot be recommended.<sup>2,13</sup>

### Panel 2: Appropriate use of topical corticosteroids for treatment of atopic eczema in primary care<sup>1</sup>

- Limit topical corticosteroid use to 3–7 days for acute eczema and up to 2–3 weeks to gain initial remission in chronic eczema
- Use the least potent topical corticosteroid that controls the condition, and review the potency and quantity of corticosteroid used regularly
- Very potent topical corticosteroids should not be used in children without specialist advice
- Limit the quantity of topical corticosteroid prescribed and the frequency of prescriptions (but ensure enough is prescribed to control the condition)

### Do tacrolimus and pimecrolimus have a role?

Recently, the topical immunosuppressive macrolides, tacrolimus (*Protopic*<sup>®</sup>) and pimecrolimus (*Elidel*<sup>®</sup>), have been launched for treatment of atopic eczema. The mechanism of action of these anti-inflammatory agents is not fully understood. However, they work in a different way to topical corticosteroids (mainly by reducing inflammation through suppression of T-lymphocyte responses) and do not cause thinning of the skin.<sup>14</sup>

Several assessments of tacrolimus and pimecrolimus have been made since their launch,<sup>15–18</sup> and NICE is also reviewing these products (appraisal expected September 2004). Despite their similar mechanism of action, the licensed indications of tacrolimus and pimecrolimus differ (see **Panel 3**), and it is likely that their role, if any, in the management of atopic eczema will also be different. At the moment, defining the place of these drugs in therapy is difficult, as trial data are limited and their long-term safety is unknown. However, the assessments published to date have all drawn similar conclusions about these drugs,

### Panel 3: Tacrolimus and pimecrolimus

#### Tacrolimus (*Protopic*<sup>®</sup>)

Tacrolimus ointment is available in two strengths (0.1% and 0.03%), both of which are licensed for second-line treatment of moderate to severe atopic eczema in adults who have not adequately responded to, or are intolerant of, conventional therapies. The lower strength is also licensed for moderate to severe atopic eczema in children aged two years and older who have not responded to conventional therapies. None of the tacrolimus trials have been conducted in the group of patients for which the product is licensed and, in practice, true topical corticosteroid 'failures' (i.e. people who require continuous corticosteroids because of a poor response or have side effects such as thinning skin) are rare, especially in primary care. However, limited trial data suggest that tacrolimus 0.1% is as effective as potent topical corticosteroids and more effective than weak topical corticosteroids such as hydrocortisone acetate 1.0%.<sup>14,17</sup>

A three-week RCT in 570 adults found that tacrolimus 0.1% twice daily was as effective as hydrocortisone butyrate 0.1% twice daily, and that both were significantly more effective than tacrolimus 0.03% twice daily.<sup>19</sup> Japanese studies have reported that tacrolimus 0.1% is as effective as the potent topical corticosteroids, betamethasone valerate 0.1% and alclometasone dipropionate 0.1%.<sup>14,17</sup> In a three-week RCT in 560 children (aged 2–15 years) both tacrolimus 0.1% and 0.03% twice daily were more effective than hydrocortisone acetate 1.0% twice daily.<sup>20</sup>

#### Pimecrolimus (*Elidel*<sup>®</sup>)

Unlike tacrolimus, which is licensed for second-line use in atopic eczema, pimecrolimus is licensed for use first-line. Pimecrolimus cream (available in one strength, 1%) is indicated for mild to moderate atopic eczema in adults and children aged two years and older, for short-term treatment of signs and symptoms and for intermittent long-term treatment to prevent flares (starting at the first appearance of eczema and continuing until clearance). However, pimecrolimus has not been compared with weak topical corticosteroids and, when it was compared with a potent topical corticosteroid (betamethasone valerate 0.1%) in a phase II study,<sup>21</sup> pimecrolimus was less effective.<sup>14,18</sup>

Three RCTs of up to 12 months' duration have investigated intermittent use of pimecrolimus for prevention of flares.<sup>22–24</sup> In all three, patients applying pimecrolimus 1% cream twice daily at the first signs or symptoms of atopic eczema had fewer flares, and hence required less topical corticosteroid, than those using a vehicle cream in the same way. However, flares were defined as severe atopic eczema requiring a moderately potent corticosteroid, and it is not known whether early, short-term use of a mild topical corticosteroid such as hydrocortisone acetate 1% before the flare became too severe might have been equally effective.<sup>14,18</sup> The three trials involved 192 adults,<sup>22</sup> 713 children aged two to 17 years<sup>23</sup> and 251 children aged three to 23 months.<sup>24</sup> However, pimecrolimus is not licensed for use in children under two years of age.

**The role of tacrolimus and pimecrolimus is limited in primary care**

**Patients and their families should be well informed about their condition and about the appropriate use of treatments**

which are at least 10 times more expensive than topical corticosteroids.<sup>14-18</sup>

In summary, **tacrolimus** is effective in atopic eczema, and could be used second-line (instead of topical corticosteroids) under certain circumstances. For example:

- If stronger corticosteroids are required on sensitive sites, such as the face
- If stronger corticosteroids are being required most of the time
- If signs of corticosteroid-induced skin damage are appearing.

However, treatment should be initiated and supervised by a specialist.<sup>14,15,17</sup>

**Pimecrolimus** is moderately effective in atopic eczema, but its place in therapy is unclear. It is licensed for use first-line, but evidence that it offers any clinical advantage over less expensive topical corticosteroids is insufficient, and a recommendation against its general use seems sensible.<sup>14,16,18</sup>

In the short-term, tacrolimus and pimecrolimus are well tolerated, with application site reactions (e.g. burning and itching) being the most common side effects. However, their long-term safety has yet to be determined. Both drugs are immunosuppressants and, although systemic absorption from topical application seems to be low, doctors should be vigilant for possible long-term side effects of immunosuppression, such as infection or malignancy.<sup>14,17,18</sup> As with all new drugs, adverse drug reactions should be reported to the Committee on Safety of Medicines, through the 'Yellow Card' scheme.

**What about other treatments?**

There is insufficient evidence to show that oral antihistamines (sedating or non-sedating) are beneficial in relieving the itch associated with atopic eczema.<sup>2,25</sup> Efforts to reduce skin dryness and inflammation, which can help symptomatically,<sup>4</sup> should be promoted instead. However, short-term use of a sedative antihistamine at night to aid sleep may be appropriate if itching is severe in certain patients.<sup>1,3-5</sup>

The use of Chinese herbal medicine became popular a few years ago, but evidence of benefit in atopic eczema is mixed,<sup>2</sup> and there are concerns about hepatotoxicity and contamination of herbal creams with corticosteroids.<sup>4</sup> Evening primrose oil was available on prescription (as *Epogam*) for the treatment of atopic eczema, but the product licence was withdrawn in 2002 because efficacy data no longer met the standards required for marketing authorisation.<sup>26</sup> Evening primrose oil is now only available as a dietary supplement.

**Conclusion**

Avoidance of exacerbating factors (where practical), and use of emollients, topical corticosteroids and oral antibiotics (where indicated) should keep atopic eczema under control in most patients. The role of the new topical products, tacrolimus and pimecrolimus, is limited in primary care. Patients and their families should be well informed about their condition and about the appropriate use of treatments to ensure they gain maximal benefits with minimal risks.

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