

## NEW PRODUCTS FOR ECZEMA

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Eczema is the most common chronic skin disease, affecting 15 to 20% children in developed countries.<sup>1</sup> Altered T cell function appears to be the primary immunological abnormality and patients have raised levels of IgE.<sup>2</sup> Most patients are managed by their general practitioner, with only a minority referred to secondary care, representing 10–20% of specialist dermatologist referrals.<sup>3</sup> One third of patients have persistent disease throughout adulthood<sup>4</sup> with a prevalence of about 2% in adults in the UK.<sup>3</sup>

Bath oils, emollients and topical corticosteroids are the mainstay of treatment. Other treatments include minimising exacerbating factors, systemic antihistamines, phototherapy, and oral immunosuppressants such as azathioprine and ciclosporin.<sup>5–6</sup> Tacrolimus and pimecrolimus are two new topical preparations widely advertised in medical and pharmaceutical journals for the treatment of eczema.

### TACROLIMUS

Tacrolimus is a macrolide lactone, an immunosuppressive agent currently used systemically to treat graft rejection in liver and kidney transplant patients. It is produced by *Streptomyces tsukubaensis* a fungus found in the soil of Mount Tsukuba in Japan.<sup>2</sup> Systemic administration causes a number of side effects including liver enzyme, renal and electrolyte disturbances, and blood disorders such as anaemia, leukocytosis and thrombocytopenia. Therefore a topical preparation has been developed.

The mechanism of action of tacrolimus in eczema is not fully understood. It is thought that tacrolimus inhibits calcium dependent signal transduction pathways in T cells via its binding to a specific cytoplasmic immunophilin. This prevents the transcription and synthesis of a number of interleukins and other cytokines such as GM-CSF and TNF- $\alpha$  all of which participate in the early immune response and are postulated to play a role in the pathogenesis of eczema.<sup>2–7</sup>

### Studies of topical tacrolimus

A number of industry sponsored studies have been conducted examining the safety and efficacy of tacrolimus ointment in patients of different ages and for different study periods.<sup>2–8–16</sup> Each study involved either a US, Canadian or European Tacrolimus Multicentre Eczema Study Group using validated tools of disease assessment. Key paediatric studies are summarised below.

### Safety and efficacy

Tacrolimus has been shown to be safe and effective in patients with moderate to severe eczema in studies ranging from three weeks to 12 months in patients from 2 to 60 years old.<sup>9–11–14</sup>

The first trial in childhood eczema involved children 7–16 years old with moderate to severe dermatitis who were randomised to twice daily treatment with tacrolimus 0.03%, 0.1% or 0.3%, or vehicle only.<sup>8</sup> The study was blinded with 180 children randomised to use the preparation for up to 22 days. There was good to excellent improvement or clearing of eczema in 67–70% of patients in all treatment groups compared with 38% in the vehicle group. No statistical differences were found between the three tacrolimus groups.

Paller *et al* conducted a 12 week randomised double blind vehicle controlled study comparing vehicle only, 0.03% and 0.1% tacrolimus ointments in children 2–15 years of age.<sup>13</sup> There was clinical improvement of  $\geq 90\%$  in 36–41% of treatment group patients compared with 7% of the vehicle only group. At least 73% of patients in either drug group demonstrated at least moderate improvement and a rapid reduction in the surface area affected by disease.

The most common adverse events described in all studies were transient burning and pruritus following application, mainly described as mild to moderate. The frequency of application site reactions seemed to reduce after the first few days as the disease improved and lesions healed. There have been no reports of skin atrophy or growth retardation. Serum levels of tacrolimus have been considered to be consistent with no or minimal absorption of tacrolimus.<sup>11–13</sup>

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## Eczema in children

- ▶ Incidence
  - Most common chronic skin disease
  - Affects 15 to 20% children in developed countries<sup>1</sup>
- ▶ Cause
  - Altered T cell function primary immunological abnormality
  - Patients have raised levels of IgE<sup>2</sup>
- ▶ Management
  - Most patients are managed in primary care, a minority are referred to secondary care
  - Bath oils, emollients and topical corticosteroids are mainstay of treatment
- ▶ Prognosis
  - A third of patients have persistent disease throughout adulthood<sup>4</sup>

### Comparison with topical corticosteroid preparations

The efficacy and safety of tacrolimus ointment (0.03% and 0.1%) have been compared with that of a mild corticosteroid, hydrocortisone acetate 1% ointment, in children (2–15 years old) with moderate to severe eczema.<sup>11</sup> Both strengths of tacrolimus ointment were found to be significantly more effective than hydrocortisone in all age groups ( $p < 0.001$ ), and 0.1% tacrolimus to be more effective than the 0.03% strength ( $p = 0.006$ ).

Tacrolimus 0.1% ointment did not subsequently become licensed for use in children despite a number of trials demonstrating its safety and efficacy, only the 0.03% strength was licensed for paediatric use. Some studies have reported that both strengths are equally effective in children,<sup>8, 13</sup> others that 0.1% tacrolimus ointment is more effective.<sup>11</sup>

A similar three week study in adult patients compared the efficacy and safety of tacrolimus ointment (0.03% and 0.1%) to 0.1% hydrocortisone butyrate (a potent topical steroid).<sup>16</sup> Tacrolimus ointment 0.1% was found to be as effective as 0.1% hydrocortisone butyrate and both were significantly more effective than 0.03% tacrolimus. Around 50% of patients in these two groups had excellent improvement or disease clearance by the end of the study. Tacrolimus 0.1% and hydrocortisone butyrate 0.1% ointments were considered equally effective, with tacrolimus offering the advantage of safety in long term use and ability to be used on the face, neck, and intertriginous areas, as it does not cause skin atrophy.

### The licensed preparation

Tacrolimus ointment was licensed in February 2002 (Protopic; Fujisawa, Staines, Surrey, UK) and is available in two strengths, 0.03% and 0.1%. Only the 0.03% strength is licensed for use in children ( $\geq 2$  years) for the treatment of moderate to severe eczema that fails to respond adequately to conventional treatments. Both are licensed for the treatment of moderate to severe eczema in adults ( $\geq 16$  years) who are not adequately responsive to or are intolerant of conventional treatments. It is recommended for prescribing only by dermatologists and physicians with extensive experience in the treatment of eczema with immunomodulating therapy.

In children, treatment should be started twice daily for up to three weeks, followed by once a day until clearance of the lesion, and then discontinued. Generally, improvement is seen within one week of starting treatment. If no signs of improvement are seen after two weeks further treatment

options should be considered. It is licensed for short term and intermittent long term treatment. Emollients should not be applied to the same area within 2 hours of applying the ointment.

Of concern is that the preparation has not actually been tested in the licensed patient groups—ie, those not adequately responsive to or intolerant of conventional treatment (tested only in patients normally maintained on conventional treatment). It has been suggested that such difficult to manage patients are rare especially in primary care, therefore the number of patients eligible for treatment is likely to be small and limited to severe cases seen by specialist dermatologists.<sup>17</sup>

### Cautions

Tacrolimus preparations are not recommended for the treatment of clinically infected areas. Systemically available tacrolimus is metabolised via the hepatic cytochrome P450 3A4 system. Although systemic exposure from topical application of tacrolimus ointment is low, the possibility of interactions cannot be completely ruled out and the concomitant systemic administration of known CYP3A4 inhibitors (eg, erythromycin, itraconazole, ketoconazole and diltiazem) in patients with widespread and/or erythrodermic disease should be with caution.<sup>7</sup> There is also a theoretical risk of vaccination failure and it is recommended that vaccines should be administered before commencement of treatment, or during a treatment free interval with a period of 14 days between the last application and the vaccination.<sup>7</sup> In the case of live attenuated vaccination, this period should be extended to 28 days or the use of alternative vaccines should be considered.<sup>7</sup>

### PIMECROLIMUS

Pimecrolimus is a lipophilic anti-inflammatory ascomycin macrolactam derivative, with a chemical structure closely resembling tacrolimus.<sup>18</sup> It is a cell selective inhibitor of the production and release of pro-inflammatory cytokines by T cells and was developed specifically for the treatment of skin conditions.

### Studies of topical pimecrolimus

A series of industry sponsored studies have examined the use of pimecrolimus using validated tools of disease assessment.<sup>4, 19–27</sup>

### Safety and efficacy

It has been reported that a large safety database of use of pimecrolimus of more than 4000 patients exists, mainly children who have been treated for up to two years.<sup>24</sup> The most frequent application site reactions include burning or feeling of warmth, others include erythema, irritation and pruritus. This generally happens early in treatment, and tends to be mild lasting 1–5 days. Meta-analysis shows no significant difference between pimecrolimus and vehicle for burning. The vehicle itself contains cetyl and stearyl alcohols and propylene glycol all of which may cause local skin reactions.

Systemic absorption has been investigated in short term (three weeks) and long term (up to 12 months) studies in adults and children, with blood levels being reported to be consistently low regardless of the extent of lesions treated or duration of treatment.<sup>6, 19–27</sup> Much of this work has however been published in posters or abstract form only.

Ho *et al* reported on the efficacy and safety of pimecrolimus in 186 children 3–23 months old with mild to moderate disease, in a six week double blind vehicle controlled phase followed by an open label 20 week phase.<sup>25</sup> Efficacy scores were clinically and statistically different by day 8. Overall median disease severity scores decreased by 82% from baseline in the pimecrolimus group by day 43 compared to 25% in controls. For head and neck the figures were 100% *v* 4%. At the start most patients had moderate to severe pruritus. By day 8, 70% of treatment group patients had no or mild pruritus compared to 37% of control patients. Caregiver's assessment was significantly different between groups at all times, and by day 43 reached complete to good control in 72% of the pimecrolimus group *v* 27% of controls ( $p < 0.001$ ). Parents' quality of life has been suggested to be improved in a similar study in children 2–17 years old.<sup>26</sup>

### Prevention studies

Several studies have concentrated on the prevention of disease flare ups. A six month study reported that flare ups were prevented in 70% of 250 children (3–23 months) who used pimecrolimus as soon as signs of eczema recurred,<sup>20, 22</sup> compared with only 32% of those using conventional treatment for flare ups (emollients and steroid creams).

Wahn *et al* performed a one year double blind controlled study in patients 2–17 years old with a primary endpoint of incidence of flares in six months.<sup>4</sup> The treatment group used pimecrolimus at the first sign of flare up, controls used vehicle. If a flare up happened, both groups used a moderately potent topical steroid. Pimecrolimus patients experienced significantly fewer flares than controls (61% *v* 34% with no flares at six months). There was no appreciable difference in incidence of adverse events between the groups, but the overall incidence of viral skin infections was slightly higher in the pimecrolimus group.

Criticisms of these prevention studies have been made, particularly with regard to the definition of "flare", which was "at least severe erythema and severe infiltration/papulation". Conventional treatment would not advocate waiting until a flare was so severe before treating. It is not known whether using a mild topical steroid such as hydrocortisone early and for the shortest possible time would be just as effective.<sup>17, 18</sup> Such a comparative study has not been performed; therefore, it is difficult to assess the clinical relevance of the steroid sparing effect of pimecrolimus. In this study many patients had to use pimecrolimus for prolonged lengths of time to gain the benefits of flare prevention.

### Comparison with topical corticosteroid preparations

In a study involving 260 adults, betamethasone valerate 0.1% (potent steroid) was compared to four different strengths of pimecrolimus (1%, 0.6%, 0.2%, 0.05%) and a vehicle control.<sup>21</sup> All strengths except 0.05% were significantly more effective than vehicle, with 1% being the most effective. This was not however as effective as betamethasone, and has not been compared with less potent topical steroids.

### The licensed preparation

Pimecrolimus (Elidel; Novartis Pharmaceuticals UK Ltd, Camberley, Surrey, UK) 1% cream was licensed in October 2002. It is indicated for patients ( $\geq 2$  years) with mild to moderate eczema for the short term treatment of signs and symptoms, and for intermittent long term treatment (up to

12 months) for the prevention of progression to flares.<sup>7</sup> A thin layer should be applied to the affected skin twice daily and rubbed in gently and completely. Each affected area should be treated until symptoms are cleared and then treatment should be discontinued. It may be used on all areas (including head and face) except mucous membranes. In long term management, treatment should start at the first appearance of signs and symptoms to prevent flares of the disease and used twice daily for as long as signs and symptoms persist. Emollients may be applied immediately after application, though use under occlusion is not recommended.

### Cautions

Like tacrolimus, pimecrolimus preparations are not recommended for the treatment of clinically infected areas. It is possible that treatment with either preparation may be associated with an increased risk of skin herpes simplex virus infection or eczema herpeticum, and an increased risk of bacterial skin infections.<sup>7</sup> However some studies have suggested that there is no significant increase in skin infections overall and bacterial infections may be reduced.<sup>10, 24</sup>

Exposure of the skin to sunlight or other sources of UV light should be minimised and avoided if possible, presumably as a precaution against any potential increase in the risk of skin cancers.<sup>28</sup> Patients should be advised on appropriate sun protection methods.

It is recommended that in patients with extensive disease, vaccinations be administered during treatment free intervals.<sup>7</sup> The effect of both treatments on the developing immune system of children has not been established. Trial data are limited and their long term safety is unknown, both are immunosuppressant agents and prescribers need to be vigilant regarding the long term potential for infection and malignancies.<sup>17</sup>

### WHERE DO THESE PREPARATIONS FIT INTO THERAPEUTIC OPTIONS?

Much has been made in the publications discussing these preparations (all drug industry sponsored) of the dangers of the use of topical steroids in children. Indeed, as eczema affects mainly children and symptoms are often chronic, selection of steroid treatment may be more complicated than in the treatment of some other skin conditions—eg, psoriasis. However, when they are used appropriately, side effects such as skin thinning and growth suppression are rarely seen, as are true topical steroid failures.<sup>1, 3, 17, 18</sup> As tacrolimus and

**Table 1** Comparative prices for corticosteroid preparations and topical immunosuppressants

Preparation	Description	Cost per 30 g*
Hydrocortisone 1%	Mild potency corticosteroid	66p
Clobetasone butyrate 0.05%	Moderate potency corticosteroid	£1.94
Betamethasone valerate 0.1%	Potent corticosteroid	£1.54
Clobetasol propionate 0.05%	Very potent corticosteroid	£2.82
Tacrolimus 0.03%	Immunosuppressant	£19.44
Tacrolimus 0.1%	Immunosuppressant	£21.60
Pimecrolimus 1%	Immunosuppressant	£19.69

\*British National Formulary No 46. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, September 2003. (£1 is approximately \$1.80 or €1.40 (January 2004))

### Key points

- ▶ Emollients and topical corticosteroids are the mainstay of treatment for eczema
- ▶ Topical steroids when used appropriately are safe and effective in most patients
- ▶ Tacrolimus 0.03% and pimecrolimus 1% ointments are new topical immunosuppressant agents licensed for use in children ( $\geq 2$  years)
- ▶ Tacrolimus 0.03% has been shown to be more effective than mild topical steroids but not more potent steroids
- ▶ Tacrolimus may be an alternative in patients vulnerable to steroid side effects or when evidence of side effects are developing
- ▶ Pimecrolimus has been tested only in mild to moderate disease and has not been compared to mild topical steroids. It is not as effective as potent steroids
- ▶ Tacrolimus and pimecrolimus have not been compared with each other
- ▶ The long term safety of both these immunosuppressant agents is not yet known
- ▶ Tacrolimus and pimecrolimus are approximately 10 times more expensive than topical steroid preparations

pimecrolimus have not been seen to cause such side effects this is the main thrust of their promotion (particularly pimecrolimus). The atrophogenic potential of pimecrolimus in comparison to medium and highly potent topical steroids (betamethasone-17-valerate 0.1% cream, triamcinolone acetonide 0.1% cream) and vehicle was tested in 16 healthy volunteers treated for four weeks.<sup>6-7</sup> Both topical corticosteroids induced a significant reduction in skin thickness measured by echography, compared to pimecrolimus or vehicle, which did not.

Opinions and recommendations have been put forward for both products.<sup>17-30</sup> Their effectiveness/cost effectiveness for eczema relative to current standard treatment is to be the subject of a UK National Institute of Clinical Effectiveness Health Technology Assessment, with results due in 2004.<sup>31</sup> This is awaited with interest.

Consensus currently suggests that tacrolimus seems to be effective in moderate to severe disease and could be used second line instead of steroids in patients where potent steroids are required in vulnerable areas such as the face or are needed on a prolonged basis as the risk of side effects is higher in these patients.<sup>17-29</sup> It may also have a role in patients where signs of steroid induced damage are appearing. Treatment should however be initiated by a specialist dermatologist.

Consensus also suggests that there is less convincing evidence for the use of pimecrolimus in the first line management of eczema and its advantages over the much less expensive steroids are not clear.<sup>17-18</sup> It is only moderately effective with most studies being conducted in patients with mild to moderate disease, and certainly not so effective as potent steroids.

Both preparations are recommended only in children aged  $\geq 2$  years despite clinical trials in younger patients. Novartis has been criticised over pimecrolimus advertisements using a picture of a baby's arm, clearly younger than the age for which the cream is licensed, the advertisement was subsequently amended.<sup>32</sup>

Both preparations are very expensive and current evidence does not justify extending the use of the products beyond the

suggested roles (Table 1). Further independent studies are needed to fill the gaps in knowledge particularly in relation to long term safety and direct comparison studies with conventional treatments involving appropriate patient selections.

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