Atopic dermatitis – Tacrolimus vs topical corticosteroid use

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Abstract
Atopic dermatitis (AD), the dermatologic manifestation of the atopic diathesis, has a variety of clinical presentations. It is a chronic and relapsing inflammatory disorder, requiring a multifaceted treatment approach. Topical corticosteroids are the backbone of therapy. However, concerns over adverse drug reactions associated with their long-term application, limit their use.

Tacrolimus, on the other hand, has been shown to be effective in stabilising the symptoms of AD in the long-term setting, without the side effects that hamper the use of topical corticosteroids. Long-term safety data up to ten years is available in the literature. Despite this, the US Food and Drug Administration (FDA)'s black box warning of possible malignancies has resulted in much debate amongst experts.

The main focus of this article is to compare the safety and efficacy of topical corticosteroids to calcineurin inhibitors, particularly tacrolimus. Furthermore, the aim is to evaluate the place of tacrolimus in the therapy of AD. A brief overview of the condition and other treatment modalities will also be discussed.

Atopic dermatitis
Atopic dermatitis (AD) is an inflammatory skin disease that is characterised by extreme pruritis and frantic scratching, which induces population, excoriation, bleeding, oozing and crustning, secondary infection and ultimately thickening or lichenification. It is a chronic disease, with periods of remission and flare-ups.

Although dermatitis can occur on any part of the body, there are typical locations of involvement that vary with age:

• In infants, extensor surfaces, cheeks and the scalp are mainly affected, but the diaper area is often spared.
• The typical localisation in childhood stages has a flexural distribution, seen mainly around the front of the elbow area, back of the knees, insides of the wrists and ankles, as well as around the neck.
• In adults, a similar pattern to that observed in childhood is seen, but it is increasingly localised and lichenified. The buttocks and hands are frequently involved.

The prevalence of AD is high, particularly in the paediatric population, and if not treated adequately AD has both physical and psychological ramifications. The incidence of AD in adults in South Africa is not recorded in the literature, but data is available regarding children and adolescents. The South African Family Practice Journal (SAFPJ) reports on a study conducted in Cape Town amongst schoolchildren 13–14 years of age. A one-year prevalence rate of 8.3%, which increased to 13.3% on follow-up, was observed in this group. In 3–11-year-old Xhosa children, a one-year prevalence rate of 1–2.5% was documented.

While AD is a disease of childhood, it can progress into adulthood. It is estimated that about 60% of childhood cases resolve by early adolescence, but dry and irritable skin often persists. Recurrences in adults are not uncommon. Concomitant atopic diseases such as asthma and allergic rhinitis, as well as family history of AD are predictive of a more persistent course.

Diagnosis
Clinical features for the diagnosis of AD are listed below. Traditionally the Hanifin and Rajika diagnostic criteria, which consist of four major and 23 minor criteria have been used as a basis of diagnosis. There is, however, lack of standardisation around clinical assessment and criteria used. Variations of the above criteria are applied by different authorities.

A prerequisite to diagnosis is evidence of itchy skin or pruritis, as well as three or more of the following major criteria:
• Typical morphology and distribution
  - Visible flexural lichenification or linearity in adults
  - Visible facial and extensor involvement in infants and children
• History of generally dry skin
• History of involvement of skin creases
• Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
• Chronic or chronically-relapsing dermatitis
• Onset before the age of two years, in patients older than four years

Listed below are some minor features of AD2,4,5,6:
• Xerosis (dry skin), dry hair and lips
• Raised serum IgE
• Wool intolerance
• Tendency toward cutaneous infections (especially *S. aureus* and *Herpes simplex*) or impaired cell-mediated immunity
• Palmar hyperlinearity
• Lateral thinning of the eyebrows
• Infant cradle cap
• Facial pallor
• Recurrent conjunctivitis
• Food allergies or intolerance
• Disease flares with emotional changes
• Increased pruritis when sweating
• Double fold of lower eyelid

A number of other dermatological manifestations may have a similar presentation to AD. It is therefore imperative that a differential diagnosis is done to exclude these dermatological conditions.5 Table I gives a list of possible differential diagnoses.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Characteristic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>Red, shiny, scaly lesions involving the diaper area in infants; absence of family history</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Lesions distributed over the extensor surfaces, scalp, buttocks; pitted nails</td>
</tr>
<tr>
<td>Irritant contact dermatitis</td>
<td>History of exposure to irritants; rash in area of exposure; damage to skin barrier; absence of family history</td>
</tr>
<tr>
<td>Insect bites</td>
<td>Symmetric distribution around the scalp, neck, face and/or extremities; erythematous crops with hypo- or hyperpigmentation; absence of family history</td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
<td>Hypersensitivity reaction following sensitisation to a substance; may be superimposed on AD</td>
</tr>
<tr>
<td>Scabies</td>
<td>Severe pruritis; J- or S-shaped burrows 5–10 mm in length on palms, soles, genitalia and between fingers</td>
</tr>
</tbody>
</table>

Treatment
The complex nature of AD as a disease which involves genetic, environmental and immunological factors necessitates individualised therapy.9 The treatment of AD is directed at symptomatic relief, skin hydration and reduction of inflammation.10 Figure 1 depicts a summary of available treatment modalities for AD.

Topical corticosteroids
Topical corticosteroids are the mainstay of therapy for acute exacerbations. The anti-inflammatory effect of topical corticosteroids in the skin is induced through various mechanisms.3,12 It has been purported that they have an antimitotic activity. This effect is attributed to their efficacy in the treatment of scaling dermatoses, as well as their ability to cause dermal thinning due to fibroblast inhibition.12 The extent to which they induce cutaneous vasoconstriction and inhibit inflammation corresponds with their potency.3,12

Topical corticosteroids can be subdivided into four groups. The classification that is used in South Africa is listed below13:
• Very potent – Group IV
• Potent – Group III
• Moderately potent – Group II
• Weak – Group I

Table II outlines the different preparations available in SA, as well as their respective potencies.

Better absorption of topical corticosteroids is observed through areas of inflammation and desquamation compared to normal skin and absorption occurs more readily through the outer dermis in infants than the skin of adults.12 In addition, increased permeability to topical corticosteroids is noted on anatomic sites with a thin epidermis, like the face, compared to thick-skinned areas, such as the palms and soles.3,12 Absorption also depends on the vehicle in the preparation, e.g. ointments result in enhanced absorption and are semi-occlusive. Creams, on the other hand, are usually less potent.12

The choice of topical corticosteroid is determined by the nature of the condition that is being treated. Generally, the best practice is to start with the lowest potency agent appropriate for the severity and to use it for as short a period of time as possible. In children, short durations of therapy with a low potency corticosteroid are recommended. Limiting high potency corticosteroids to areas other than the face and the inner aspects of thighs and axillae, as well as once daily applications reduce the incidence of side effects.3,12 The use of topical corticosteroids should be discontinued once the skin condition has resolved.5,12 Clinical trials have shown that these agents are safe and effective for AD when used for up to four weeks.5

Although topical corticosteroids are safer compared to systemic
**Atopic dermatitis diagnosis**

**Active treatment**
- **Topical corticosteroids**
  Mainstay or first line for acute flare-ups

- **Topical calcineurin inhibitors**
  Second line agents

- **Coal tar**
  Alternative for patients with mild to moderate AD; has anti-inflammatory and antipruritic effects; may be useful in lichenified lesions

**Supportive treatment**
- **Emollient creams**
  To treat xerosis and reduce the need for corticosteroids

- **Sedating antihistamines**
  Dubious role in pruritis, but indicated for sleep disturbance and co-morbid allergies

- **Antibiotics**
  For *Staphylococcus* infections

- **Systemic agents:**
  - Ciclosporin
  - Azathioprine
  - Systemic corticosteroids, short-term
  - Mycophenolate mofetil
  - Interferon gamma
  - IV immunoglobulins
  For severe, resistant cases

- **Phototherapy:**
  - UVA
    For acute flares
  - UVB
    For chronic disease
  - PUVA
    For chronic, severe disease

- **Nonpharmacologic:**
  - Dietary restrictions
  - Allergen reduction
  - Psychological approaches

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Figure 1: Available treatment modalities for atopic dermatitis

* There are mixed results or limited evidence regarding the efficacy due to lack of proper randomised trials

UVA – ultraviolet type A
UVB – ultraviolet type B
PUVA – Psoralen potentiated ultraviolet A
glucocorticoids, systemic side effects can occur, particularly with super potent and potent drugs, or extensive use of lower potency agents.12 Adverse effects of topical corticosteroids are discussed in more detail later in this article.

**Calcineurin inhibitors**

Tacrolimus and pimecrolimus are classified as calcineurin inhibitors.5,15 This article focuses on tacrolimus, which is a macrolide lactone immunosuppressant. It exerts an inhibitory effect on T-lymphocyte activation and also modulates the release of inflammatory mediators from skin mast cells and basophils.10,15,16 Primarily, it inhibits the phosphatase activity of calcineurin. Calcineurin is an essential component in the series of events that are necessary in the early stages of T-cell activation. In summary, tacrolimus modulates the key cellular mediators that are imperative in AD pathogenesis.9,15,16

Pharmacokinetically, tacrolimus is a relatively large and highly lipophilic molecule with a strong affinity for the skin. It exhibits rate-limiting absorption. As the skin heals, there is a proportionate reduction in the absorption of tacrolimus.9 Although tacrolimus penetrates the skin, systemic absorption is minimal.9,10 In clinical trials, systemic blood levels were found to be below the limit of quantification.1,10 Serum concentrations were shown to be minimal in a 3-week, phase II, randomised, double-blind, multicentre study, which was designed to investigate absorption from 0.03%, 0.3% and 0.1% tacrolimus preparations.1 Based on this, systemic side effects are expected to be minimal, if not absent.9,15 More detail on adverse effects is supplied later in this article.

**Comparative data on topical corticosteroids vs tacrolimus**

A number of studies have been conducted in an effort to establish the safety and efficacy of tacrolimus compared to either vehicle base or different potencies of topical corticosteroids. Outlined below are some of these studies, as well as their results.

Kapp et al reported on two short-term, corticosteroid-controlled trials. These were double-blind, randomised, multicentre, comparative studies.6 Refer to Table III for a summary of the study design and results in the adult arm.

In adults, there was rapid improvement of symptoms across all study arms. Also noted was an improvement in disease status and this was progressive in all three groups as assessed by the modified Eczema Area and Severity Index (mEASI). There was no statistically significant difference in mEASI score between tacrolimus 0.1% and hydrocortisone butyrate 0.1%. Improvement was also noted in the tacrolimus 0.03% group, although significantly less than in the other two groups, p < 0.5

<table>
<thead>
<tr>
<th>Potency</th>
<th>Examples</th>
<th>Dosage form</th>
<th>Adult/paediatric appropriateness</th>
<th>Body location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very potent – Group IV</td>
<td>Clobetasol propionate 0.05%</td>
<td>Cream, ointment, scalp lotion</td>
<td>Adults</td>
<td>Resistant, thick lesions; palms, soles and scalp</td>
</tr>
<tr>
<td></td>
<td>Diflucortolone valerate 0.3%</td>
<td>Ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potent – Group III</td>
<td>Beclometasone dipropionate 0.025%</td>
<td>Cream</td>
<td>Adults</td>
<td>Thick lesions; palms, soles and scalp</td>
</tr>
<tr>
<td></td>
<td>Betamethasone valerate 0.1%</td>
<td>Cream, ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Betamethasone dipropionate 0.05%</td>
<td>Cream, ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diflucortolone valerate 0.1%</td>
<td>Ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flucinolone acetonide 0.025%</td>
<td>Cream, ointment, gel</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate 0.05%</td>
<td>Cream</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate 0.005%</td>
<td>Ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone butyrate 0.1%</td>
<td>Cream, ointment, lotion, topical emulsion</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone aceponate 0.1%</td>
<td>Cream, milk, ointment, fatty ointment</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate 0.1%</td>
<td>Cream, ointment, lotion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately potent – Group II</td>
<td>Betamethasone valerate 0.05%</td>
<td>Cream</td>
<td>Adults and children</td>
<td>Extensive body involvement, excluding face and thin-skinned areas</td>
</tr>
<tr>
<td></td>
<td>Clobetasone butyrate 0.05%</td>
<td>Ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weak – Group I</td>
<td>Hydrocortisone acetate 0.5% and 1%</td>
<td>Cream, ointment</td>
<td>Adults, children and infants</td>
<td>Face, folds, genitals and for extensive use</td>
</tr>
</tbody>
</table>

Table II: Topical corticosteroids available in South Africa12,13,14
for both comparisons. Table IV gives a summary of results in the paediatric arm.

In children, both tacrolimus treatment groups showed a statistically significant improvement compared to the hydrocortisone acetate group, \( p \leq 0.001 \) for both comparisons. Tacrolimus 0.1% was significantly better compared to the 0.03% formulation, \( p < 0.05 \).

The overall results of these two studies show that in the short-term tacrolimus is as effective as moderately potent to potent topical corticosteroids and more effective compared to mild or weak potency topical corticosteroids. Tacrolimus was also shown to have similar efficacy to a moderately potent steroid in a phase III, randomised, open-label study comparing tacrolimus 1% to betamethasone valerate 0.12% over three weeks.

Long-term data is also available. In a 6-month comparative trial, Reitamo et al investigated the difference in efficacy between tacrolimus 1% and hydrocortisone butyrate 1% applied to the trunk and extremities, as well as hydrocortisone acetate 1% applied to head and neck areas. Table V tabulates the results.

A greater number of patients responded to tacrolimus compared to the hydrocortisone arm. The difference was statistically significant with \( p < 0.001 \). There was also an improvement noted on the health-related quality of life (HRQOL) with tacrolimus compared to the topical corticosteroids.

In other long-term, noncomparative studies in which both adults and children were observed for one year, prolonged tacrolimus use showed progressive and sustained improvement in symptoms of AD.

### Adverse effects

The main adverse drug reaction observed with the use of tacrolimus is transient skin burning. Generally, this is mild to moderate in intensity and does not necessitate withdrawal of treatment, as it diminishes over time. Other side effects include mild, transient pruritis and skin erythema. All these side effects are limited to areas of application.

As a topical immunomodulatory agent, tacrolimus carries the theoretical risk of increasing skin infections, like Herpes simplex infections, eczema herpeticum, fungal dermatitis, furunculosis, or warts. Some studies did report a

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**Table III: Different strengths of tacrolimus ointment vs hydrocortisone butyrate**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Duration – 3 weeks</th>
<th>Number of participants – 570 adult patients</th>
<th>AD severity – moderate to severe</th>
<th>Regimen – twice daily applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Tacrolimus 0.1%</td>
<td>Tacrolimus 0.03%</td>
<td>Hydrocortisone butyrate 0.1%</td>
<td></td>
</tr>
<tr>
<td>Sample size (n)</td>
<td>191</td>
<td>193</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td>Mean mEASI reduction</td>
<td>77.3%</td>
<td>67.5%</td>
<td>73.4%</td>
<td></td>
</tr>
<tr>
<td>PGE</td>
<td>49.2%</td>
<td>37.6%</td>
<td>51.4%</td>
<td></td>
</tr>
<tr>
<td>DS</td>
<td>85.0%</td>
<td>79.9%</td>
<td>79.2%</td>
<td></td>
</tr>
<tr>
<td>Skin burning</td>
<td>8.7%</td>
<td>6.8%</td>
<td>1.2%</td>
<td></td>
</tr>
</tbody>
</table>

PGE – physician’s global evaluation of clinical response: percentage of patients with 90% improvement or more; mEASI – modified Eczema Area and Severity Index; DS – percentage of patients with ≥ 50% improvement in disease status

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**Table IV: Different strengths of tacrolimus ointment vs hydrocortisone acetate**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Duration – 3 weeks</th>
<th>Number of participants – 560 children, age 2–15 years</th>
<th>AD severity – moderate to severe</th>
<th>Regimen – twice daily applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Tacrolimus 0.1%</td>
<td>Tacrolimus 0.03%</td>
<td>Hydrocortisone acetate 1%</td>
<td></td>
</tr>
<tr>
<td>Sample size (n)</td>
<td>186</td>
<td>189</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Mean mEASI reduction</td>
<td>75.9%</td>
<td>65.8%</td>
<td>37.3%</td>
<td></td>
</tr>
<tr>
<td>PGE</td>
<td>48.4%</td>
<td>38.5%</td>
<td>15.7%</td>
<td></td>
</tr>
<tr>
<td>DS</td>
<td>83.5%</td>
<td>80.2%</td>
<td>51.4%</td>
<td></td>
</tr>
<tr>
<td>Skin burning</td>
<td>5.6%</td>
<td>1.1%</td>
<td>1.2%</td>
<td></td>
</tr>
</tbody>
</table>

PGE – physician’s global evaluation of clinical response: percentage of patients with 90% improvement or more; mEASI – modified Eczema Area and Severity Index; DS – percentage of patients with ≥ 50% improvement in disease status
higher incidence of viral skin infections during initial treatment with tacrolimus compared to corticosteroids; other studies not.9,10,16 Overall, long-term treatment (6–12 months) is not associated with an increased prevalence of cutaneous infections; therefore tacrolimus does not seem to impair cell-mediated immunity.9,10,16,18 However, it is important to note that application of tacrolimus preparations to infected areas is not recommended.9,13,16

Acne is one problem for which a causal relationship with long-term use of the drug cannot be ruled out.16 Flushing, especially with alcohol ingestion, has also been reported in a number of studies.11,13,16

An increased risk of malignancies is another concern with tacrolimus.13,15,16 As such, there is a black box warning against the use of tacrolimus placed by the FDA in 2005 due to lack of long-term safety data at the time and the potential risk for the development of malignancies, mainly lymphoma and skin cancer. This was based on information derived from animal studies.2,5,19

However, to date there is no data to suggest that tacrolimus is associated with an increased risk of cancer in either children or adults.9 No increased risk of nonmelanoma skin cancer was found in posthoc reviews, neither was squamous cell skin cancer reported in any clinical trials with tacrolimus.9,10,16,18 A literature search also did not produce any evidence to confirm any malignancy risk, but some authors are still concerned.4,10,18

Nevertheless, tacrolimus carries a warning for minimal exposure to sunlight or UV light, as a precautionary measure against local malignancies.3,18 Alternatively, patients can be counselled to use sun protection creams.2,4,10,15,18

Adverse drug reactions associated with the use of corticosteroids range from skin atrophy, striae, telangiectasia, acne, glaucoma, adrenocortical insufficiency and, in extreme cases, Cushing’s syndrome.5,12,16,17 However, there is no conclusive evidence that correctly used topical agents cause significant systemic side effects.5,18 In fact, literature suggests that when used for periods up to four weeks, topical corticosteroids are safe and effective for the treatment of AD flare-ups.8 Conversely, it is the long-term use or overuse that is associated with adverse effects.2,5

Regarding skin atrophy, no cases were reported for tacrolimus. On the contrary, in a 12-month study of tacrolimus 0.1% in adults, some patients experienced reversal of symptoms. It was unclear whether this was due to absence of steroids or directly attributable to tacrolimus.9

The atrophogenic potential of tacrolimus was specifically investigated in a randomised, phase II, double-blind, placebo-controlled trial with 14 AD patients and 12 healthy subjects. Tacrolimus 0.1%, 0.3%, betamethasone valerate 0.1%, and vehicle were applied twice, on day 1 and again 3–4 days later, to nonaffected abdominal skin and occluded with bandages. Skin thinning was only observed with betamethasone.9

In contrast, four 16-week randomised trials with topical corticosteroids failed to show any clinically significant skin thinning. Concerns of patients and parents about topical corticosteroid use may be out of proportion to the true risk.2 In summary, many experts agree that skin thinning with topical corticosteroids is minimal if they are used intermittently and correctly.2,4,5,18

Table V: Tacrolimus 0.1% compared to hydrocortisone-based preparations9,10,17

<table>
<thead>
<tr>
<th>Study design</th>
<th>Duration – maximum 6 months</th>
<th>Number of participants – 972 adults</th>
<th>AD severity – moderate to severe</th>
<th>Regimen – twice daily applications</th>
<th>Primary end point – ≥ 60% improvement in mEASI at 3 months</th>
<th>The mean % reduction in mEASI and median reduction in DQLI were also measured at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Tacrolimus 0.1%</td>
<td>Hydrocortisone butyrate 1%</td>
<td>Hydrocortisone acetate 1% – head and neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size (n)</td>
<td>487</td>
<td>485 combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point reached</td>
<td>72.6%</td>
<td>52.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean mEASI reduction</td>
<td>73%</td>
<td>62%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponders</td>
<td>52 patients (10.7%)</td>
<td>124 patients (25.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DQLI median decrease</td>
<td>74.3%</td>
<td>69.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mEASI - modified Eczema Area and Severity Index; DQLI - Dermatology Quality of Life Index (a higher score represents a lower quality of life)

In South Africa, tacrolimus (Protopic®) is registered for the treatment of moderate to severe atopic dermatitis in adolescents ≥ 16 years and adults. The 0.03% strength is to be applied initially as a thin layer twice daily to affected skin

Discussion

The above results suggest that tacrolimus 0.1% is as effective as potent topical corticosteroids and more effective than mild topical corticosteroids, such as hydrocortisone acetate 1%, for treating atopic dermatitis in the short term. Long-term efficacy and safety are even more promising. Having looked at the different studies, as well as the adverse effect profile of both topical corticosteroids and tacrolimus, the question arises as to the place in therapy for tacrolimus in AD.

In South Africa, tacrolimus (Protopic®) is registered for the treatment of moderate to severe atopic dermatitis in adolescents ≥ 16 years and adults. The 0.03% strength is to be applied initially as a thin layer twice daily to affected skin
until the lesion clears. If this fails or results are inadequate, then the 0.1% preparation should be started. Treatment should be stopped if there is no improvement after three weeks. In patients 2–15 years old, the 0.03% strength may be applied twice daily for up to three weeks, then the application should be reduced to once daily until the lesion clears. \(^{11}\)

Topical corticosteroids are effective in most patients\(^{5,11}\) and given the fact that tacrolimus 0.1% is about 1.4 to 3.6 times more expensive per 30 g than moderately potent and potent original steroid preparations,\(^{20}\) the cost-effectiveness of topical tacrolimus vs steroids still needs to be established.\(^9\)

Several authorities recommend that tacrolimus be used as a second-line therapy, for moderate to severe AD in the following scenarios:

- For face and neck areas where high potency steroids would be required to control symptoms.\(^{2,10,18}\)
- Where long-term treatment with steroids is required.\(^{10,18}\)
- In patients with evident signs of steroid toxicity.\(^8\)
- In patients who are resistant to topical corticosteroids (rarely seen).\(^2,3,10,18\)
- In patients who are intolerant to conventional therapies.\(^2,3,10,18\)

The National Institute for Health and Clinical Excellence (NICE) gives the following recommendation: “Topical tacrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged two years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.” NICE also recommends that topical corticosteroids are to be used as first-line treatment for episodic worsening (flare-ups) of atopic eczema. They should be used intermittently, in order to reduce exposure to corticosteroids.\(^{21}\)

**Conclusion**

Tacrolimus offers an alternative to the treatment of moderate to severe atopic dermatitis and steroid-resistant AD. It may be useful for atopic dermatitis at sensitive sites such as the face, where the use of potent topical steroids carries a high risk of thinning of the skin and telangiectasia.\(^1\) Tacrolimus 0.1% may also be useful for patients who depend on the constant use of potent steroids. The cost-effectiveness, as well as long-term risk of infections and cancers remain to be determined.\(^4,10,18\)

References

20. Monthly Index of Medical Specialties (MIMS). 2010; 50(7)