Atopic dermatitis: tacrolimus vs. topical corticosteroid use

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Abstract

Atopic dermatitis (AD), the dermatological 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 are available in the literature. Despite this, the US Food and Drug Administration (FDA) black box warning of possible malignancies has resulted in much debate among 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 AD therapy. A brief overview of the condition and other treatment modalities will also be discussed.

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Introduction

Atopic dermatitis (AD) is an inflammatory skin disease that is characterised by extreme pruritis and frantic scratching. This induces papulation, excoriation, bleeding, oozing and crusting, secondary infection, and ultimately, thickening or lichenification.[1-4] It is a chronic disease, with remission periods and flare-ups.[3,5]

Although dermatitis can occur on any part of the body, there are typically affected locations that vary with age.[4-6]

- In infants, extensor surfaces, cheeks and the scalp are mainly affected, but the nappy area is often spared.
- In childhood, typical localisation 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. If not treated adequately, AD has both physical and psychological ramifications.[3,5,6] The incidence of AD in adults in South Africa is not recorded in the literature, but data are available regarding children and adolescents. The *South African Family Practice Journal* reported on a study conducted in Cape Town among schoolchildren, aged 13-14 years. A one-year prevalence rate of 8.3%, which increased to 13.3% on follow-up, was observed in this group. In three- to 11-year-old Xhosa children, a one-year prevalence rate of 1-2.5% was documented.[4]

While AD is a childhood disease, 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.[2,3] Concomitant atopic diseases, such as asthma and allergic rhinitis, as well as family history of AD, are predictive of a more persistent course.[2,5]

Diagnosis

Traditionally, the Hanifin and Rajika diagnostic criteria, which consist of four major and 23 minor criteria, have been used as a basis of diagnosis.[6] However, there is a lack of standardisation around the clinical assessment and criteria that are used.[3] 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:[3-6]

- Typical morphology and distribution: visible flexural lichenification or linearity in adults, and

- visibly affected facial and extensor areas in infants and children.
- History of generally dry skin.
- History of skin creases being affected.
- Personal or family history of atopy (asthma, allergic rhinitis and 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 AD features:[2,4-6]

- Xerosis (dry skin), dry hair and lips
- Raised serum immunoglobulin E (IgE)
- Wool intolerance
- Tendency toward cutaneous infections (especially *Staphylococcus 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 present in a similar way to AD. Therefore, it is imperative that a differential diagnosis is carried out to exclude these dermatological conditions.[5] Table I gives a list of possible differential diagnoses.

Table I: Selected differential diagnoses of atopic dermatitis[2,4,7,8]

Diagnosis	Characteristic features
Seborrhoeic dermatitis	Red, shiny, scaly lesions affecting the nappy area in infants. An absence of family history.
Psoriasis	Lesions distributed over the extensor surfaces, scalp and buttocks. Pitted nails.
Irritant contact dermatitis	History of exposure to irritants. Rash in area of exposure. Damage to skin barrier. Absence of family history.
Insect bites	Symmetric distribution around the scalp, neck, face and/or extremities. Erythemous crops with hypo or hyperpigmentation. Absence of family history.
Allergic contact dermatitis	Hypersensitivity reaction following sensitisation to a substance. May be superimposed on atopic dermatitis.
Scabies	Severe pruritis; J- or S-shaped burrows, 5-10 mm in length on palms, soles, genitalia and between fingers.

Treatment

Individualised therapy is necessary because of the complex nature of AD as a disease which involves genetic, environmental and immunological factors.[9] The treatment of AD is directed at symptomatic relief, skin hydration, and reduction of inflammation.[10] Figure 1 depicts a summary of available AD treatment modalities.

Topical corticosteroids

Topical corticosteroids are the mainstay of therapy for acute exacerbations. Their anti-inflammatory effect on 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 treating 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 South African classification is listed below:[13]

- Very potent: Group IV
- Potent: Group III
- Moderately potent: Group II
- Weak: Group I.

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

Better absorption of topical corticosteroids is observed in areas of inflammation and desquamation compared to normal skin, and absorption occurs more readily through the outer dermis in infants than through the skin of adults.[12] In addition, increased permeability to topical corticosteroids is noted at anatomical 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 carrying the preparation, for expample 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, best practice is to start with the lowest potency agent that is appropriate to the severity, and to use it for as short a time as possible. In children, short durations of therapy with low-potency corticosteroids are recommended. The adverse effect profile of higher potency topical corticosteroids has limited their use in children, as well as for treatment of facial areas. Limiting high-potency corticosteroids applied to areas other than the face and the inner aspects of the thighs and axillae, as well as to 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, when used for up to four weeks, these agents are safe and effective in the treatment of AD.[5]

Although topical corticosteroids are safer compared to systemic glucocorticoids, systemic side-effects can occur, particularly with super-potent and potent drugs, or extensive use of lower-potency agents.[12] The adverse effects of topical corticosteroids are discussed in more detail in this article.

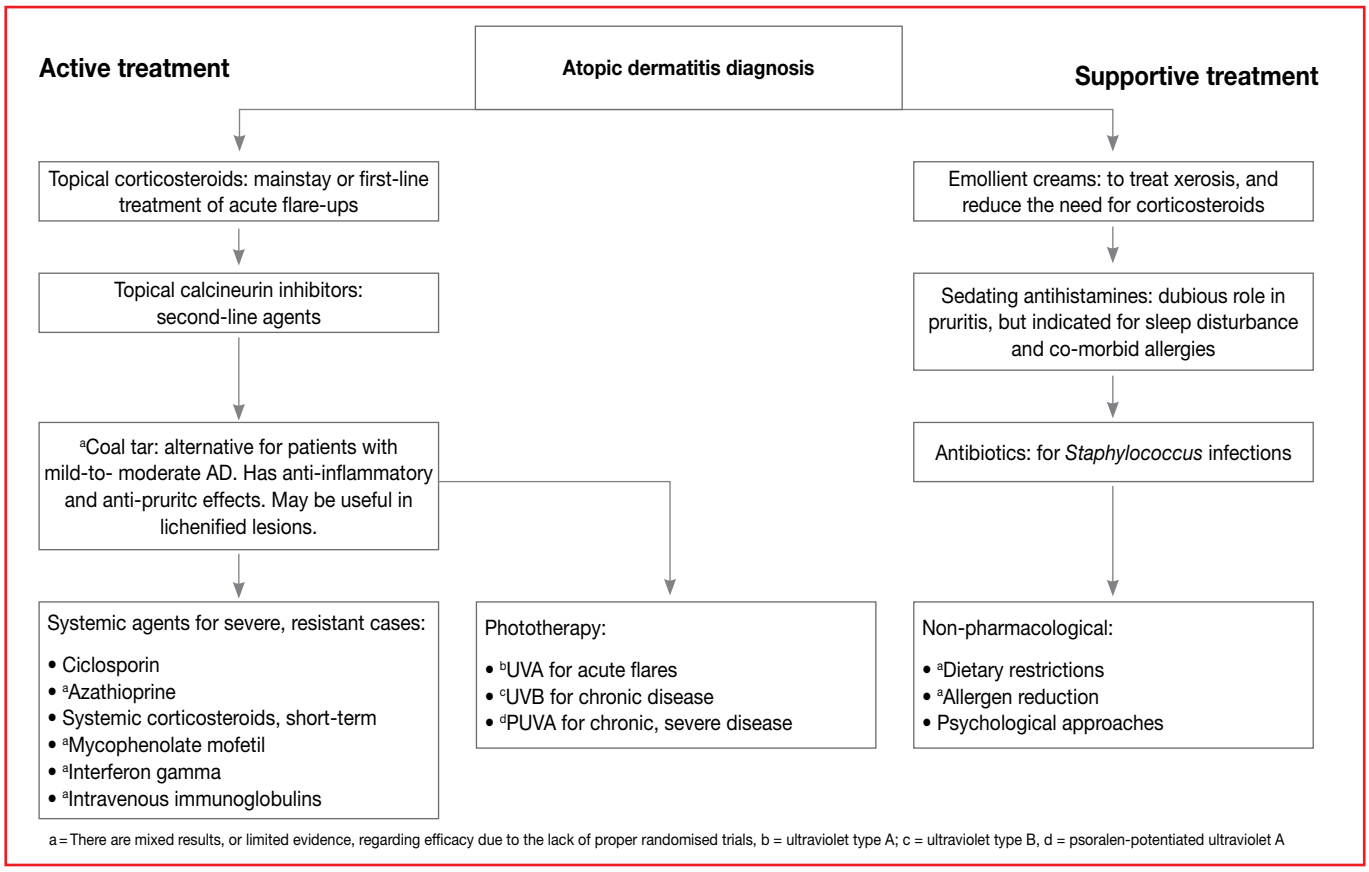

Figure 1: Available treatment modalities for atopic dermatitis[2-5,7,10,11]

Table II: Available topical corticosteroids in South Africa[12-14]

Potency	Examples	Dosage form	Adult/paediatric appropriateness	Body location
Very potent: Group IV	Clobetasol propionate 0.05%	Cream, ointment or scalp lotion	Adults	Resistant, thick lesions. Palms, soles and scalp.
	Diflucortolone valerate 0.3%	Ointment		
Potent: Group III	Beclometasone dipropionate 0.025%	Cream	Adults	Thick lesions. Palms, soles and scalp.
	Betamethasone valerate 0.1%	Cream or ointment		
	Betamethasone dipropionate 0.05%	Cream or ointment		
	Diflucortolone valerate 0.1%	Fatty ointment		
	Fluocinolone acetonide 0.025%	Cream, ointment or gel		
	Fluticasone propionate 0.05%	Cream		
	Fluticasone propionate 0.005%	Ointment		
	Hydrocortisone butyrate 0.1%	Cream, ointment, lotion, or topical emulsion		
	Methylprednisol-one aceponate 0.1%	Cream, milk, ointment or fatty ointment		
	Mometasone furoate 0.1%	Cream, ointment or lotion		
Moderately potent: Group II	Betamethasone valerate 0.05%	Cream	Adults and children	Body area is affected extensively, excluding face and thin skinned areas.
	Clobetasone butyrate 0.05%	Ointment		
Weak: Group I	Hydrocortisone acetate 0.5% and 1%	Cream or ointment	Adults, children and infants	Face, folds, and genitals. Also for extensive use.

Calcineurin inhibitors

Tacrolimus and pimecrolimus are classified as calcineurin inhibitors.[5,15] This article focuses on tacrolimus, 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 three-week, phase II, randomised, double-blind, multicentre study, which was designed to investigate absorption of 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 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.[9] 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 the 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-value < 0.5 for both comparisons).[9] 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-value ≤ 0.001 for both comparisons). Tacrolimus 0.1% was significantly better compared to the 0.03% formulation (p-value < 0.05).[9]

Table III: Different strengths of tacrolimus ointment vs. hydrocortisone butyrate[9,16]

Study design	Duration: Three weeks Number of participants: 570 adult patients Atopic dermatitis severity: Moderate to severe Regimen: Twice-daily applications		
Treatment	**Tacrolimus 0.1%**	**Tacrolimus 0.03%**	**Hydrocortisone butyrate 0.1%**
Sample size (n)	191	193	186
Mean [a]mEASI reduction	77.3%	67.5%	73.4%
[b]PGE	49.2%	37.6%	51.4%
[c]DS	85.0%	79.9%	79.2%
Skin burning	8.7%	6.8%	1.2%

a = Modified eczema area and severity index, b = physician's global evaluation of clinical response: percentage of patients with 90% improvement or more, c = percentage of patients with ≥ 50% improvement in disease status

Table IV: Different strengths of tacrolimus ointment vs. hydrocortisone acetate[9,16]

Study design	Duration: Three weeks Number of participants: 560 children aged 2-15 years Atopic dermatitis severity: Moderate to severe Regimen: Twice-daily applications		
Treatment	**Tacrolimus 0.1%**	**Tacrolimus 0.03%**	**Hydrocortisone butyrate 0.1%**
Sample size (n)	186	189	185
Mean [a]mEASI reduction	75.9%	65.8%	37.3%
[b]PGE	48.4%	38.5%	15.7%
[c]DS	83.5%	80.2%	51.4%
Skin burning	5.6%	1.1%	1.2%

a = Modified eczema area and severity index, b = physician's global evaluation of clinical response: percentage of patients with 90% improvement or more, c = percentage of patients with ≥ 50% improvement in disease status

Table V: Tacrolimus 0.1% vs. hydrocortisone-based preparations[9,16,17]

Study design	Duration: Maximum 6 months Number of participants: 972 adults Atopic dermatitis severity: Moderate to severe Regimen: Twice-daily applications Primary end point: ≥ 60% improvement in [a]mEASI at 3 months The mean percentage reduction in mEASI and median reduction in [b]DQLI was also measured at 3 months	
Treatment	**Tacrolimus 0.1%**	**Hydrocortisone butyrate 1%: trunk and extremities Hydrocortisone acetate 1%: head and neck**
Sample size (n)	487	485 combined
Primary end-point reached	72.6%	52.3%
Mean [a]mEASI reduction	73%	62%
Non-responders	52 (10.7%)	124 (25.6%)
[b]DQLI median decrease	74.3%	69.2%

a = Modified eczema area and severity index; b = Dermatology quality of life index (a higher score represents a lower quality of life)

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.[9] Tacrolimus was also shown to have a 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.[16]

Long-term data are also available. In a six-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.[17] Table V tabulates the results.

A greater number of patients responded to tacrolimus, compared to the hydrocortisone arm. The difference was statistically significant, with a p-value of < 0.001.[17] An improvement was also noted on the health-related quality of life (HRQOL) with tacrolimus, compared to the topical corticosteroids.[16]

In other long-term, non-comparative studies, in which both adults and children were observed for one year, prolonged tacrolimus use showed progressive and sustained improvement in AD symptoms.[9]

Adverse effects

Transient skin burning is the main adverse drug reaction observed with use of tacrolimus.[2,5,9] Generally, this is mild to moderate in intensity, and does not necessitate withdrawal of treatment as it diminishes over time.[9,13,16] Other side-effects include mild, transient pruritis, and skin erythema. All these side-effects are limited to the application areas.[9,16]

As a topical immunomodulatory agent, tacrolimus carries the theoretical risk of increasing skin infections, such as herpes simplex infections, eczema herpeticum, fungal dermatitis, furunculosis, or warts.[10,13,15,18] Some studies reported a higher incidence of viral skin infections during initial treatment with tacrolimus, compared to corticosteroids. Other studies did not.[9,10,16] Overall, long-term treatment (six to 12 months) is not associated with an increased cutaneous infection prevalence. 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.[9,13,18]

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.[13,15,16] As such, there is a black box warning against tacrolimus, issued by the US Food and Drug Administration (FDA) in 2005, against the potential risk of development of malignancies, mainly lymphoma and skin cancer. This was done because of a lack of long-term safety data at the time, and is based on information derived from animal studies.[2,5,19]

However, to date, there are no data to suggest that tacrolimus is associated with an increased risk of cancer in either children or adults.[9] No increased risk of non-melanoma skin cancer was found in post hoc reviews, and neither was squamous cell skin cancer reported in any clinical trials using tacrolimus ointment.[9,10,16] 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 about minimal exposure to sunlight or ultraviolet light, as a precautionary measure against local malignancies.[5,18] Alternatively, patients can be counselled to use sun-protection creams.[5,9,10,15,18]

Adverse drug reactions associated with the use of corticosteroids include skin atrophy, striae, telan-giectasia, acne, glaucoma, adrenocortical insufficiency, and in extreme cases, Cushing 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 of up to four weeks, topical corticosteroids are safe and effective in treating AD flare-ups.[5] Conversely, it's the long-term use or overuse that is associated with adverse effects.[2,5]

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

Tacrolimus' atrophogenic potential was specifically investigated in a randomised, phase II, double-blind, placebo-controlled trial with 14 AD patients and 12 healthy subjects. Tacrolimus 0.1% and 0.3%, bethamethasone valerate 0.1%, and the vehicle were applied twice, on day one, and again three to four days later, to unaffected 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. Patients' and parents' concerns about topical corticosteroid use may be out of proportion to the true risk.[2] In summary, many experts agree that skin thinning arising from use of topical corticosteroids is minimal, if they are used intermittently and correctly.[2,4,5,18]

Interestingly, in the phase III bethamethasone 0.12% comparative study mentioned earlier, the overall safety ratings by patients were 88% for tacrolimus, and 91% for the cortisone preparation.[16]

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 examined the different studies, as well as the adverse effect profile of both topical corticosteroids and tacrolimus, the therapeutic positioning of tacrolimus in AD has to be queried.

In South Africa, tacrolimus (Protopic®) is registered for use in children from the age of two years (0.03% strength), as well as in adults and adolescents from the age of 16 years (both 0.03% and 0.1% strengths). 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 applied. If there is no improvement after three weeks, treatment should be stopped. In patients aged two to 15, the 0.03% strength may be applied twice daily for up to three weeks, and then the application reduced to once daily until the lesion clears.[13]

Topical corticosteroids are effective in most patients.[5,18] Given the fact that tacrolimus 0.1% is about 1.4-3.6 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.[4]

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.[9,10,18]
- Where long-term treatment with steroids is required.[10,18]
- In patients with evident signs of steroid toxicity.[18]
- In patients who are resistant to topical corticosteroids (rarely seen.)[2,9,10,18]
- In patients who are intolerant to conventional therapies.[2,9,10]

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 2 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 AD and steroid-resistant AD. It may be useful in treating AD at sensitive sites such as the face, where the use of potent topical steroids carries a high risk of skin thinning 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 in the South African context.[4,18]

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