Review Article

PROACTIVE THERAPY IN ATOPIC DERMATITIS

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ABSTRACT

Atopic dermatitis is a chronic inflammatory skin condition with a relapsing nature. Typical treatment is reactive for acute lesions and visible flares. However, normal-looking non-lesional skin in atopic dermatitis has been shown to be immunobiologically dysfunctional, characterised by subclinical inflammation. Such ongoing, sub-clinical inflammation provides the rationale for the concept of 'preventive' or 'proactive' therapy of atopic dermatitis, with long-term intermittent use of anti-inflammatory agents in addition to regular moisturising. Regular, intermittent use of topical corticosteroids and calcineurin inhibitors have both been shown to reduce flare rates in moderate to severe atopic dermatitis, with a good safety profile.

INTRODUCTION

Atopic dermatitis (AD) is a highly pruritic, chronic inflammatory skin condition characterised by a relapsing nature with periods of acute worsening (flares) alternating with periods of relative quiescence.[1] AD is common, occurring in approximately 5% of adults and 20% of children and generates significant morbidity.[1,2] Typical treatment is 'reactive' for visible flares and acute lesions: responding to flare-ups using anti-inflammatory agents short term on lesional skin. Such reactive treatment, coupled with daily moisturising, may be adequate in milder AD and in cases with infrequent relapses.

A better understanding of the immunology of the skin has led to strategies that attempt to embrace long-term control of the recurrent flares. It has become clear that some individuals will benefit from a more 'proactive' method aimed at reducing flares and stabilising the skin barrier with more long-term use of anti-inflammatory agents. This mirrors the concept of 'controller therapy' in inflammatory atopic conditions such as asthma and allergic rhinitis (AR). Proactive therapy in AD entails the use of anti-inflammatories – either topical corticosteroids or topical calcineurin inhibitor – applied to previously affected skin on a long-term, scheduled and intermittent basis, coupled with daily moisturisers used on all areas.[2] Proactive therapy should always be preceded by intensive topical anti-inflammatory therapy until control is achieved. The aim of such proactive therapy is to prolong lesionless periods after active treatment. The concept of proactive therapy has been extensively studied during the past 10–15 years and is widely accepted for its efficacy and safety, such that it now forms part of major dermatology guidelines worldwide.[3,4]

This aim of this article is to describe the rationale and supportive evidence for proactive therapy using topical anti-inflammatories for AD, and to outline its practical application.

RATIONALE FOR PROACTIVE THERAPY: THE CONCEPT OF ONGOING IMMUNOBIOLOGICAL DYSFUNCTION IN ATOPIC DERMATITIS

Normal-looking non-lesional skin in AD has been shown to be immunobiologically dysfunctional and characterised by invisible 'sub-clinical' inflammation. Non-lesional skin has been demonstrated to have:

- A defective skin barrier characterised by increased trans-epidermal water loss.[5–7]
- A 60% reduction in the fraction of long-chain fatty acids in the lipid bilayer of the stratum corneum compared to healthy skin.[8]
- Activation of venules and low-grade lymphocytic infiltration.[9]
- Upregulation of high-affinity IgE receptors on the surface of epidermal Langerhans cells.[10]

Ongoing subclinical inflammation, leading to the potentially frequent 'resurgence' of flares, forms the basis of the rationale for proactive therapy. With recent evidence of transcutaneous sensitisation through the skin with a defective skin barrier, the concern, especially in infants, is that ongoing allergen sensitisation via 'normal'-looking skin may occur owing to the diffuse skin-barrier defect in children with AD. A recently published study by Leung et al has shown that children with AD and food allergies have significantly increased transepidermal water loss in non-lesional skin.[11] A further concern is the risk of infectious complications such as *Staphylococcus aureus* (*S aureus*) overgrowth in large areas of skin with subclinical barrier defects.

SUPPORTIVE EVIDENCE FOR PROACTIVE THERAPY IN ATOPIC DERMATITIS

Whereas initial evidence for proactive therapy was published 20 years ago,[12] the concept was adopted in Europe only approximately ten years ago and even more recently in the United States. Studies have been performed using topical

corticosteroids (both moderately potent and potent) and calcineurin inhibitors (tacrolimus), but no head-to-head trials between the two anti-inflammatory types have been performed to date.

STUDIES USING INTERMITTENT TOPICAL CORTICOSTEROIDS AS PROACTIVE THERAPY

Both Fluticasone propionate (0.05%) and Methylprednisolone aceponate (0.1%) have been tested in double-blind randomised placebo-controlled designs; however, none exceeded 20 weeks' duration.

In a study published in 2002, Hanifin et al compared intermittent dosing with 0.05% fluticasone cream with its vehicle base in 348 patients over 20 weeks; and found a 7.7 times reduction in flare rate in the active treatment group, with no significant skin atrophy reported.[13] The maintenance treatment was applied twice weekly for 20 weeks.

Another large randomised study, published in 2003, compared fluticasone propionate cream (0.05%) and fluticasone propionate ointment (0.005%) in 295 patients with moderate to severe AD. This study found that using either preparation twice weekly in combination with daily emollient use significantly reduced the risk of flares and extended the time of remission during a 16-week trial.[14] The flare-free period under proactive treatment was more than twice as long as with reactive treatment, and the number of recurrences was 5.8 times lower in the cream group and 1.9 times lower in the lower-strength ointment group compared with the placebo.

Looking specifically at children with moderate to severe AD, Glazenburg et al studied the twice-weekly application of fluticasone propionate (0.005%) cream in a 16-week, placebo-controlled trial of 75 children, published in 2009. This study found the flare rate in the proactive group to be less than half that of the reactive group.[15]

In a study by Fukuie et al in 2016, children with moderate to severe AD were maintained with intermittent topical corticosteroids (0.12% betamethasone valerate to the limbs and 0.1% hydrocortisone butyrate to face and trunk) for 12 months.[16] They were also tested for house-dust mite (HDM) sensitisation during the study period. In the actively treated group, the severity of AD was reduced compared to the placebo and the aeroallergen-specific IgE levels did not increase during the year of treatment.

In a study involving a 16-week trial by Peserico et al published in 2008, methylprednisolone aceponate (0.1%) cream and placebo were given to adults with AD.[17] In this study, the active group experienced a significant reduction in flares, though the placebo group also had an unusually low flare rate. This led to a questioning of the initial severity of the eczema in the participants.

STUDIES USING INTERMITTENT CALCINEURIN INHIBITORS AS PROACTIVE THERAPY

To date, all published studies for proactive therapy with calcineurin inhibitors have been performed with tacrolimus ointment; none with pimecrolimus.

In 2008, a double-blind, randomised placebo-controlled study published by Wollenberg et al examined the use of tacrolimus proactively twice weekly for 12 months in adult patients with AD (n = 224) (after an initial open-label induction phase of tacrolimus twice daily for six weeks).[18] Time to eczema flare was 142 days in the tacrolimus group versus 15 days in the placebo group, $p < 0.001$. The proactive group also showed significantly fewer flares and a reduced duration of flares (flares on 12.5% versus 31.5% of treatment days, $p < 0.001$.) The adverse event profile was similar between tacrolimus and placebo.

In a European study looking at more than 250 children with mild to severe AD, also published in 2008, proactive treatment with 0.03% tacrolimus over 12 months reduced the number of flares significantly (50.4% of the proactively treated group and only 29.6% of the placebo group remained flare-free).[19]

In 2008, Paller et al tested a three-times weekly application of tacrolimus (0.03%) in 105 children with moderate to severe AD in the maintenance phase of a placebo-controlled study. The median time to first flare was 116 days in the active group versus 31 days in the placebo group – a significant improvement.[20]

Similarly, in 2008, Breneman et al tested a thrice-weekly application of tacrolimus (0.03% for children or 0.1% for adults) in a randomised 40-week maintenance phase of 197 patients with moderate to severe AD. The median flare-free time in the proactive group was 169 days versus 43 days in the placebo group.[21]

SAFETY OF PROACTIVE TOPICAL ATOPIC DERMATITIS TREATMENT

To date, no side-effects have been reported to be more common than in placebo controls in studies with tacrolimus in up to one year of proactive therapy; nor have any been reported in topical corticosteroids used for up to 20 weeks.[13–21] Neither of the drugs has shown an increase in cutaneous infections. Skin atrophy has not been demonstrated with the use of intermittent proactive fluticasone propionate therapy.[13–15]

Long-term studies of reactive treatment with tacrolimus have shown that systemic absorption is minimal;[22] moreover, reactive treatment with tacrolimus up to four years showed no increased likelihood of infections or cumulative adverse events.[23]

NOTE: Despite the excellent safety profile, patients should be warned of the potential side-effects of topical steroid overuse, such as thinning of the skin; and of the potential side-effects of topical tacrolimus therapy, such as burning or stinging. The latter can be reduced significantly by ensuring that flare-ups are well under control before topical calcineurin inhibitors are commenced.

PRACTICAL APPLICATION: INDICATIONS FOR AND BASIC PRINCIPLES OF PROACTIVE THERAPY IN ATOPIC DERMATITIS

Significant evidence now indicates that proactive therapy in AD with intermittent topical corticosteroids or tacrolimus reduces the frequency of flare-ups and increases the number of flare-free

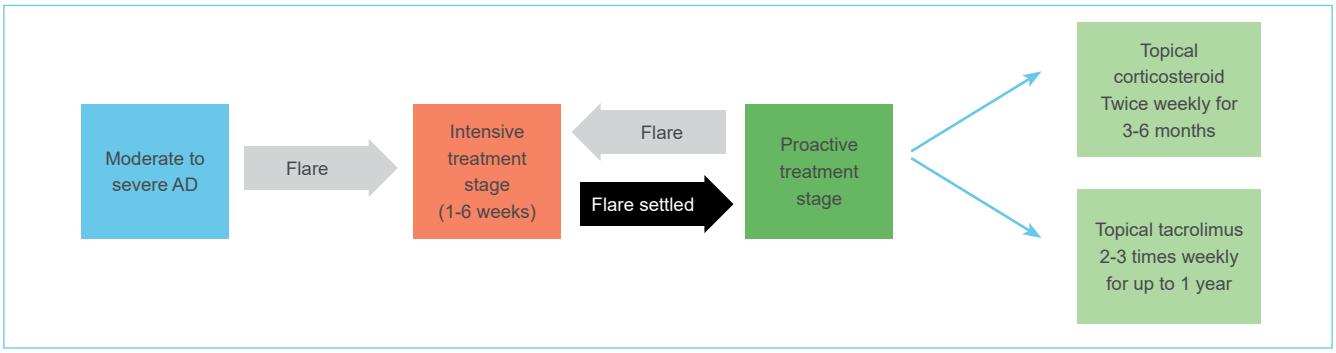

Figure 1: Proactive treatment in AD

days. Tacrolimus has recently been licensed specifically for the intermittent long-term proactive treatment of AD in adults and children.

Such proactive therapy is most suitable for patients with moderate to severe eczema with frequent exacerbations (occurring four or more times a year). It is usually not necessary for those with mild eczema.

Importantly, proactive therapy should always be preceded by an intensive course of topical anti-inflammatory therapy until all lesions have mostly disappeared. Despite the clearance of visible eczema, low-dose intermittent therapy is continued, at least twice weekly. On the days of proactive treatment, topical calcineurin inhibitors should be applied twice a day and topical corticosteroids should be applied once a day to all skin prone to relapse. In addition, moisturisers should be applied daily to the entire body and face.

Disease frequency, severity and site need to be taken into account when advising on a proactive strategy most suitable for each patient. The availability of various anti-inflammatories (e.g. tacrolimus, which is not readily available in state clinics in South Africa) and cost factors also need to be taken into consideration when choosing an appropriate proactive strategy.

PROACTIVE TOPICAL THERAPY IN ATOPIC DERMATITIS GUIDELINES

The evidence-based use of proactive topical anti-inflammatories has been integrated into recent guidelines for the management of AD in both Europe and the United States.

In the European Dermatology Forum Guidelines for Treatment of AD published in 2018, the evidence grade and strength of recommendation for the application of topical corticosteroids twice weekly to reduce relapses for up to 20 weeks are 1b and A. Similarly, the evidence grades for the application of tacrolimus twice to three times weekly to reduce relapses for up to one year are 1b and A.[3]

The American Academy of Dermatology Association (AADA) suggests that:

> Continued use of either topical corticosteroids (1–2 times/week) or topical calcineurin inhibitors (2–3 times/week) after disease stabilisation, to previously involved skin, is recommended to reduce subsequent flares or relapses. (Level of evidence 1, strength of recommendation A).[4]

The South African guideline on the management of AD does not currently have a section on proactive therapy, only a one-line mention of the possible benefit of 'weekend' steroid therapy in long-term management.[24] There is a need for an update inclusive of proactive treatment in order for the guideline to conform to the international guidelines. Proactive AD management would be of great potential benefit to so many of our local patients.

ADDITIONAL STRATEGIES IN PROACTIVE THERAPY FOR ATOPIC DERMATITIS

MOISTURISERS

Regular moisturiser use on all skin is strongly recommended throughout reactive and proactive therapy for AD: it may reduce the signs of inflammation, barrier dysfunction, itch and lichenification.[25] In those individuals with moderate to severe AD, moisturisers may be inadequate to prevent flares sufficiently. They are therefore recommended in combination with proactive anti-inflammatory therapy. Hundreds of moisturisers are available and the exact choice is beyond the scope of this article. A brief summary below reiterates some of the important characteristics of a good moisturiser suitable for AD sufferers:[26]

- It should provide an occlusive barrier for the skin to retard transepidermal water loss and protect the skin from irritants. Examples include lanolin, petrolatum, paraffin and silicone.
- It should help the skin to retain moisture: humectants attract water vapour to moisturise the skin (similarly to natural moisturising factors). They include glycerol, glycerin, urea, sorbitol and alpha-hydroxyl acids.
- It should contain an emollient, because emollients fill in the cracks between desquamating corneocytes in order to soften and smooth the skin. Examples include collagen, elastin, glyceryl stearate and shea butter.
- It should be free from sodium laureth sulphates and other irritants or sensitisers.

There is currently no convincing evidence of efficacy of one type of moisturiser over another.[25,26] The choice of moisturiser should be based on fulfilment of the basic characteristics outlined above, taking into account physician preference, patient preference and cost. Several newer brands of moisturisers contain specialised ingredients that target the replacement of ceramides or contain

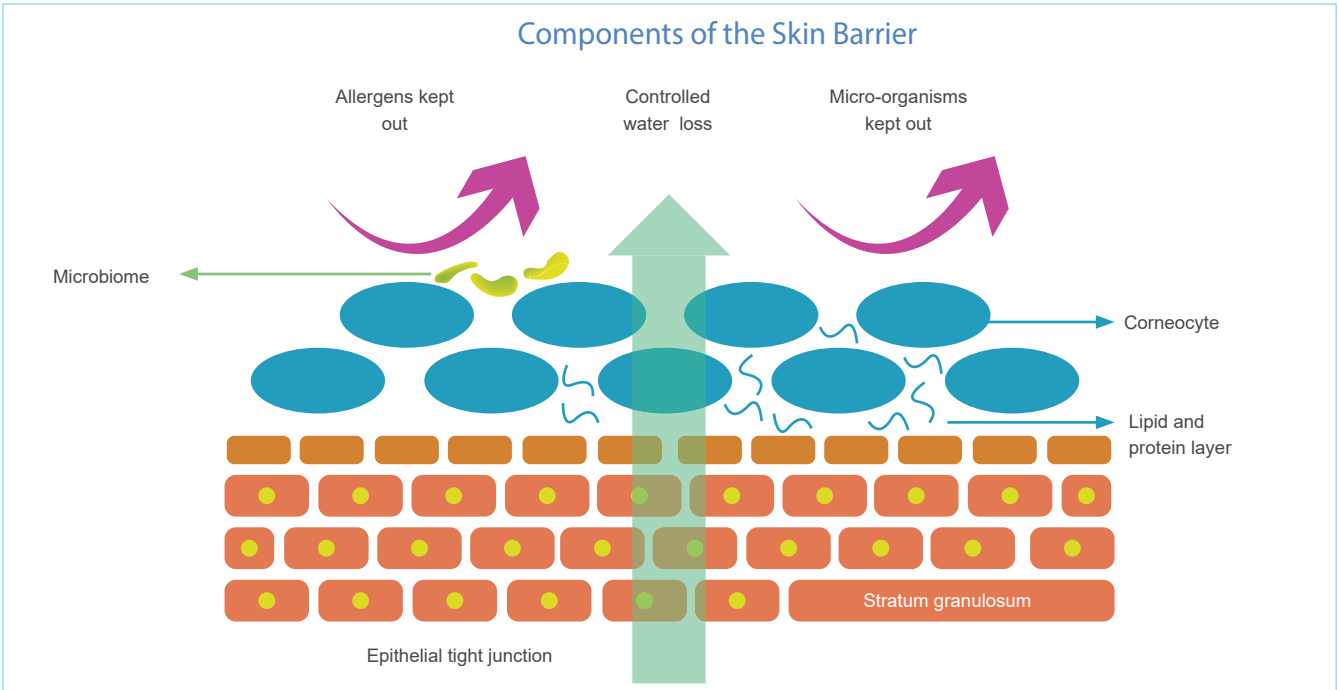

Figure 2: The microbiome as a part of the skin barrier

natural moisturising factors such a filaggrin degradation products. These ingredients add potential benefit but also add significantly to the cost.

PROACTIVE USE OF ANTISEPTICS

Up to 90% of patients with eczema are colonised with *Staphyloccocus aureus*,[27–28] partly because of a defective innate immune system in eczematous skin. An overgrowth of *S aureus* can cause a worsening of AD; it can also lead to potential infections such as impetigo, folliculitis or farunculitis. Part of a long-term treatment aim in AD should be a reduction in colonisation with *S aureus*. Topical antibiotic use is discouraged, owing to the risk of antibiotic resistance. Long-term use of topical antiseptics is generally well tolerated, including chlorhexidine.[29] The use of hypochlorite or potassium permanganate in the bath also has a good antiseptic action. Overt infection with *S aureus* needs to be treated promptly.

SKIN MICROBIOME MANIPULATION AS PART OF PROACTIVE THERAPY

The human skin hosts a diverse symbiotic microbial community known as the microbiome, which helps to maintain skin health, immunological integrity and barrier function (see Figure 2).

The loss of diversity of the healthy microbial community and an overgrowth of 'pathogenic' bacteria such as *S aureus* have been associated with the potentiation of skin disorders such as AD.[29] The relationship between microbiome and skin heath has led to attempts to manipulate the microbiome as part of AD maintenance treatment, in order to reduce flares and inflammation. Topical skin formulations containing certain bacterial lysates have been shown potentially to modulate skin immunity and restore skin microbial diversity, in this way helping as a maintenance strategy in chronic AD.[30]

CONCLUSION

For those individuals with mild AD, daily emollient use and the reactive use of topical anti-inflammatory therapy may be sufficient. In those with moderate to severe AD, proactive therapy with an intermittent topical anti-inflammatory in addition to moisturising should be considered.

Data from several placebo-controlled studies have shown that both topical corticosteroids and tacrolimus inhibitors have good efficacy in proactive eczema therapy, leading to reduced flares and better quality of life (QoL), without significant side-effects. In addition, proactive management allows the patient to be actively involved in controlling their skin rather than passively waiting for the next flare.

The concept of proactive therapy now has an established role in AD management and it should be adopted in patients with moderate to severe AD with frequent relapses. Proactive therapy should always be combined with moisturiser use. In addition, treatment may need to be stepped up temporarily for flare-ups. The choice of anti-inflammatory depends on many factors, including cost and availability.

DECLARATIONS OF CONFLICT OF INTEREST

The author declares no conflict of interest.

This article has been peer reviewed.

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