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*Review Article*

# Reactive and proactive treatment in atopic dermatitis: Long-term disease control

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## ABSTRACT

Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disease. The condition is prevalent worldwide affecting children more than the adult population. AD is associated with a significant adverse impact on a patient's physical, psychological, and social life. Control of symptoms and disease activity and minimizing the number of flares are the goal of AD treatment. Available treatment options for AD include topical and/or systemic therapy. Despite significant advancements in the systemic treatment landscape including biologics and tyrosine kinase inhibitors, topical therapy remains valuable in the treatment of AD. In this article, we cover the pathophysiology of AD in brief along with the definitions of reactive and proactive approach of treatment. The concept of proactive treatment with topical therapy to control the disease and prevent flares is discussed along with the supporting published evidence.

**Keywords:** Emollients, Reactive treatment, Proactive treatment, Topical corticosteroids, Topical calcineurin inhibitors

## INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease which worldwide affects between 5% and 20% of all children and up to 5% of the adult population, with the highest incidence in affluent countries.[1,2] The symptoms are an unrelenting itch, chronic eczematous, and oozing skin lesions and an increased number of infections in the skin. There are many different definitions of the disease, but the Hanifin and Rajka criteria from 1980 are very comprehensive. The criteria consist of the major criteria that are (1) pruritus, (2) typical morphology and distribution of the skin lesions, (3) chronic or chronically relapsing disease, and (4) a personal history of atopy, where patients must have three or more of the symptoms. Furthermore, the patient should have 3 or more of the 23 minor criteria for this disease [Table 1].

The relapsing nature of the disease is for many patients, the most severe symptom. They can treat the disease, but often the disease relapses immediately after cessation of therapy, much to the frustration and agony of the patients.

Thus, treatment has two goals: (1) to make the disease and its symptoms subside and (2) to control the disease and minimize the number of flares. Treatment modalities can be topical and/or systemic. In this paper, we will focus on topical therapy and how the concept of proactive treatment can be used to control the disease and prevent flare-ups.

## COMORBIDITIES OF AD AND QUALITY OF LIFE

AD adversely affects their physical, psychological, and social well-being, casting its shadow over various aspects of their lives, including education, professional endeavors, and leisure activities. This condition permeates every facet of a patient's health trajectory, making control of the disease paramount for the patients.

Individuals fighting and suffering from AD face an elevated risk of psychiatric comorbidities, particularly those with severe AD since childhood. This includes an increased risk of developing attention deficit hyperactivity disorder[3,4] depression, suicidal thoughts, and suicide.[5] These burdens extend not only to the patients themselves but also to their caregivers. There is growing evidence that disturbed sleep quality, driven by the incessant itch associated with AD, serves as a pivotal causal factor for these psychiatric comorbidities. In addition, inflammation and the itch itself might potentially lead to permanent changes in the brain, contributing to the emergence of psychiatric symptoms.[6,7] Furthermore, AD can lead to the stigmatization of those afflicted.[8]

AD significantly alters the life trajectories of those affected. Research from Denmark has revealed that individuals

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**Table 1:** Hanifin and Rajka criteria for atopic dermatitis.

| | |
|---|---|
| Major criterions | Itch, typical morphology, and distribution, chronic or chronically relapsing dermatitis, personal or family history of atopy |
| Minor criterions | Xerosis, ichthyosis vulgaris, positive skin prick test, elevated serum immunoglobulin E, early age of onset, tendency to cutaneous infections, hand-and-foot eczema, nipple eczema, cheilitis, recurrent conjunctivitis, Dennie–Morgan infraorbital furrow, keratoconus, anterior subcapsular cataract, orbital darkening, facial pallor, anterior neck folds, itch when sweating, intolerance to wool, perifollicular accentuation, worsening with environmental factors. White dermographism. |

grappling with early and severe AD experience diminished educational attainment. However, it is essential to note that the absolute numbers involved are relatively small, and the potential influence of familial factors remains unclear.[9] AD escalates the risk of sick leave and the utilization of disability pensions.[10] In adults, AD imposes a substantial economic burden due to heightened health-care costs when compared to a matched healthy cohort.[11]

Furthermore, AD patients face an increased risk of comorbidities. This encompasses a heightened risk of other type II inflammatory conditions such as asthma, rhinoconjunctivitis, and eosinophilic esophagitis. In addition, there appears to be a heightened risk of certain cardiovascular diseases, although ongoing debates explore whether this association might be attributable to lifestyle factors among AD patients or the inflammatory nature of the disease itself.[12,13]

## PATHOPHYSIOLOGY OF AD

AD arises from a complex interplay of a compromised skin barrier function, a type II inflammatory response within the skin, and alterations in the skins' microbiome. The precise mechanisms and intricate pathways driving AD are the subject of intense ongoing research and the basis for understanding the proactive treatment approach for the disease, and we provide a concise and up-to-date overview here.[14]

For many AD patients, a genetic predisposition contributes to xerosis and a weakened skin barrier function due to mutations in the FLG gene that encodes filaggrin. Filaggrin serves as a crucial structural protein in the keratinocytes' cytoskeleton within the epidermis. It also plays a central role in the generation of natural moisturizing factor that serve to retain moisture in the skin, regulate skin pH, modulate the activity of protease inhibitors that safeguard corneodesmosome binding between keratinocytes, and offer photoprotection through the production of trans-urocanic acid.[15] The absence of filaggrin can lead to skin irritation, inflammation, and subsequent downregulation of filaggrin expression.[16] Other structural proteins such as loricrin, involucrin, and hornerin may be lacking in AD due to inflammation-induced downregulation, further compromising the skin barrier, as may mutations in SPINK5 which encodes the protease inhibitor LEKTI, which also protects the integrity of the corneodesmosomes. Moreover, a decrease in lipid lamellae, particularly the shortage of ω-hydroxy fatty acid sphingosine, contributes to barrier impairment.[14]

The inflammatory response observed in AD-affected skin is a complex interplay involving keratinocytes and immune cells, with a particular emphasis on lymphocytes. This inflammation represents a type II response characterized by a Th2/Th22-dominated pattern, marked by increased proliferation and activation of type 2 innate lymphoid cells (ILC2), immunoglobulin E-producing B cells, and eosinophils.[17] The significance of Th2 cytokines and type II inflammation is underscored by the therapeutic effectiveness of monoclonal antibodies targeting key players such as interleukin (IL)-4, IL-13, and thymic stromal lymphopoietin (TSLP) that are archetypal Th2 cytokines associated with type II inflammation.[18,19] While the precise origins of the inflammatory process remain debated, it is increasingly evident that a group of alarmins originating from epidermal keratinocytes, including IL-33, high mobility group box 1 (HMGB1), and TSLP, play pivotal roles.[20] In addition, the cytokine IL-31 has garnered attention as the "itch-cytokine," although it also possesses inflammatory properties, as evidenced by clinical trials with anti-IL-31 antibodies, which have demonstrated notable effects on AD-related itch symptoms.[21]

It is very important to understand that, in AD patients, not only the lesional skin is affected, but also non-lesional skin demonstrates a significantly increased number of inflammatory cells compared to healthy skin and indeed an increased production of inflammatory cytokines, especially the $Th_2$-cytokines and the skin specific chemokines. This ongoing inflammatory reaction has also been coined as microinflammation.

Thus, even in the so-called healthy or non-lesional skin of AD patients, there is an ongoing inflammatory reaction, and thus AD patients would in many instances require continuous treatment, and this is the basis for the concept of proactive treatment.

## TREATMENT OF AD

The target for the treatment of AD is the inflammatory reaction in the skin as described above. However, regardless of the severity of AD or the specific anti-inflammatory treatment chosen, a fundamental aspect of therapy involves the daily application of generous amounts of moisturizer. This practice alleviates xerosis, diminishes transepidermal water loss, and facilitates the restoration of the skin barrier.[22] By restoration of the skin barrier, emollient therapy also contributes to

the reduction of skin inflammation, thereby decreasing the necessity for topical anti-inflammatory treatments. In addition, alongside emollients, it is advisable to incorporate educational programs and strategies for avoiding clinically significant allergens into the treatment regimen.[23]

Although there is an almost exponential growth in new drugs aiming at specific inflammatory pathways in the skin, including the biologics such as dupilumab, tralokinumab, and lebrikizumab that block the IL4/IL13 pathway, or Janus Kinase Inhibitors which inhibits the intracellular signaling of the inflammatory cytokines, or even the drugs that are tested on the IL-31 pathway and the OX40 pathway, applying either topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs), is usually well tolerated, simple, often cheap, and with a minimum of adverse effect, and actually often used together with the new and advanced therapies.

### TCS

TCSs have remained the cornerstone of topical anti-inflammatory therapy for AD across all age groups for over six decades. They continue to stand as the first-line option for managing inflammation.[22] Typically, TCSs are introduced into the treatment regimen when disease control cannot be achieved solely through the daily application of emollients and proper skin care practices.[22]

The mechanism of action of TCS hinges on steroid receptors located within the cell cytoplasm. Upon ligand binding, these receptors translocate to the nucleus, where they orchestrate a dual effect: the inhibition of pro-inflammatory signals and the initiation of anti-inflammatory signals, thus curtailing the secretion and impact of pro-inflammatory mediators.[24]

TCSs are categorized into four potency levels, determined through vasoconstriction assays. The selection of potency is contingent upon factors such as patient age, the location of AD lesions, and the severity of the condition.[23]

Prolonged or excessive TCS use may lead to adverse events. There exists an inherent risk of developing contact dermatitis to the preparations of either the corticosteroid itself (rare) or the constituents of the formulation of the vehicle itself (the ointment or cream).[25] Hypopigmentation is a well-documented side effect, although it may also, which is more often the case, be attributed to the inflammatory reaction itself (post-inflammatory hypopigmentation). Reversible hypertrichosis may also follow the use of topical steroids. Application of TCS to facial areas carries the risk of perioral dermatitis, rosacea-like eruptions, and acne.[25] Skin atrophy, including striae, especially in areas with thin skin such as the axillae and the groin is another recognized side effect, that may occur with any TCS, irrespective of their potency.[23] Risk factors for skin atrophy include the use of high-potency agents, occlusive application, long-term usage, application to thinner skin regions, and advanced patient age.[22]

While systemic side effects stemming from TCS are uncommon, they may include hypothalamic-pituitary-adrenal (HPA) axis suppression.[26]

### TCIs

TCIs exert their therapeutic effect by inhibiting calcineurin-dependent T-cell activation, thereby preventing the transcription of pro-inflammatory cytokines.[27,28] These agents possess both anti-inflammatory and anti-pruritic properties, distinct from the side effects associated with TCSs. The most frequently encountered adverse effect is local discomfort at the application site, characterized by sensations of burning, erythema, and pruritus, particularly in the case of tacrolimus application. However, these symptoms commonly abate within a few days of initiating treatment. The two main TCIs in use are Tacrolimus and pimecrolimus.

Tacrolimus 0.03% exhibits a potency similar to mild TCS (Groups I and II), whereas tacrolimus 0.1% corresponds to TCS of intermediate potency (Groups II and III). On the other hand, pimecrolimus has demonstrated an efficacy comparable to low-potency TCS (Groups I and II).[29,30] Notably, long-term treatment with pimecrolimus has demonstrated a substantial steroid-sparing effect, as observed in studies where it was used reactively whenever AD activity was present.[31]

For pimecrolimus, similar adverse effects may manifest during the initial phase of treatment. However, no significant disparity in these symptoms between pimecrolimus and the vehicle agent has been established.[27,32] Both short-term and long-term treatments have not exhibited any alterations in paraclinical measurements.[27] Concerns regarding the potential impact on immunization with vaccines have been raised, but extended studies spanning 2- and 5-year pimecrolimus have shown that children develop normal antibody titers to common vaccine antigens, with no heightened risk of serious adverse events or infections observed.[33,34]

In 2006, the Pediatric Advisory Committee of the US (Food and Drug Administration) implemented a "black box" warning for tacrolimus ointment and pimecrolimus cream due to a lack of long-term safety data and concerns regarding potential malignancy development.[35] However, two decades after the introduction of TCIs, comprehensive long-term safety data from 4-year to 10-year tacrolimus studies, as well as a 5-year pimecrolimus study, has emerged. Importantly, no increased risk of lymphoma or other malignancies has been substantiated, leading to the removal of the black box warning.[33,36-39]

## WHAT IS REACTIVE AND PROACTIVE TREATMENT

Reactive treatment is the application of a topical drug either TCS or TCI, at the first signs of active disease in the skin. The treatment is upheld for as long as needed to

make the symptoms subside. Once the lesions are gone, treatments are tapered down or stopped directly. Both during the period of active treatment and later moisturizers must be applied liberally and daily. Proactive therapy is to continue the use of the active drug (CS or TCI) regularly twice or three times a week, once the symptoms have subsided, either on the entire skin surface or in the regions where the lesions usually appear, combined with the use of moisturizers daily.

The initial study on proactive therapy involved 125 adults and 247 children who were randomized to receive either intermittent fluticasone propionate (twice per week) or a vehicle control.[40] After a stabilization phase with daily fluticasone propionate use, there was a 16-week maintenance phase with twice-weekly application. Among adults receiving proactive treatment, the likelihood of AD relapse was 7.0 times lower than in the vehicle-treated group. Pediatric patients exhibited an 8.1-fold reduction in AD relapse likelihood compared to the vehicle-treated group. The median time to relapse for the vehicle group was 4.7 weeks, whereas it could not be calculated for the intermittent fluticasone propionate group due to the majority maintaining control at 20 weeks. Importantly, there were no reported cases of skin atrophy in the intermittent fluticasone propionate group, nor other adverse events.[40]

The first study was a 12-month randomized, vehicle-controlled study involving 257 adults with mild-to-severe AD who were randomized to receive either 0.1% tacrolimus or a vehicle control. All patients underwent an initial treatment phase with twice-daily application of tacrolimus to affected areas for up to 6 weeks. Once the investigator global assessment score reached <2, patients entered a disease control period and were randomized to proactive therapy (twice weekly) with either 0.1% tacrolimus or (IGA) vehicle control. Results demonstrated that proactive treatment with tacrolimus significantly reduced the number of disease exacerbations, and the percentage of days requiring DE treatment, and extended the time to the first disease exacerbation (142 vs. 15 days) compared to the vehicle group. No serious adverse effects were observed during the 12-month study period.[23]

Numerous subsequent studies have explored proactive therapy with both TCS and TCI, culminating in a meta-analysis of 9 randomized controlled trials. This meta-analysis, conducted in 2011, included four studies with the proactive use of tacrolimus, four with fluticasone propionate, and one with methylprednisolone aceponate. It indicated that each agent, when used proactively, was significantly more effective at preventing flares compared to their respective vehicle agents. In addition, the meta-analysis suggested that TCS might be more efficacious than tacrolimus.[41] Importantly, the authors addressed potential bias stemming from shorter durations of TCS trials, emphasizing a significant inverse relationship between efficacy and the duration of proactive therapy, which indicated that TCS superiority was not influenced by shorter trial durations.[41] Nevertheless, it remains unclear whether the benefits of proactive TCS therapy can be sustained for over a year, given the available data. The meta-analysis reported no serious adverse events in the tacrolimus group and no cases of skin atrophy in any of the TCS studies. However, Hanifin *et al.*'s study identified biochemical signs of adrenal suppression in 4.5% of children.[40]

A 2018 meta-analysis encompassing 522 pediatric patients with atopic eczema treated with TCS revealed that only 2% of patients using low-potency TCS demonstrated reversible, biochemical HPA axis suppression after daily use for 4 weeks. As the potency of TCS increased, there was a higher proportion of children displaying biochemical signs of HPA axis suppression, though the differences between potency groups were not statistically significant.[42] A separate study from 2000 investigated HPA axis suppression in 35 children with AD who had used TCS for extended periods. Results were consistent, indicating rare HPA axis suppression in children using low or moderately potent TCS, but a higher occurrence in those utilizing potent TCS either alone or in conjunction with oral, intranasal, or inhaled glucocorticosteroids.[43] However, a recent registry study from Denmark reported an increased risk of type 2 diabetes associated with TCS exposure.[44] Difference between proactive and reactive treatment is given in Table 2.

**Table 2:** Proactive versus reactive treatment.

| | Proactive treatment | Reactive treatment |
|---|---|---|
| Time to flare up | Significantly prolonged | Often very low |
| Side effects* | No difference | No difference |
| Amount of topical used to control the disease | Lower | Higher |
| Overall | Proactive is the superior technique to control the disease. For some patients, it may prove difficult to follow the regimen, and the use should always be held up against the severity and the extent of the symptoms. If the entire surface of the skin is to be treated, systemic treatment might be considered. | |

A study involving Danish and U.K. adult cohort indicated positive association between TCS and type 2 diabetes; however, there is no information on whether it was proactive or reactive treatment.[44]

## CONCLUSION

The evidence suggests that TCSs may be employed for proactive therapy with low risks of side effects, although not entirely devoid of risks, and the benefits should be weighed carefully against the potential risks. Some studies have

assessed the potential economic benefits of proactive therapy with tacrolimus, indicating that it may not lead to extra costs in moderate AD and could even be cost saving for severe AD compared to reactive therapy.[45,46] Furthermore, proactive therapy has shown improvements in the quality of life for both children and adults, mainly in the context of tacrolimus use.[23,45,47,48] The sense of "gaining control" over the disease and experiencing prolonged periods without eczema have been proposed as contributing factors to this improvement.[49,50] However, long-term safety data for proactive therapy remains limited, and the challenge lies in addressing the chronic, unpredictable, and recurrent nature of AD, as well as determining the appropriate duration of treatment.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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### Conflicts of interest

Dr. Christian Vestergaard is on the editorial board of the Journal.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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