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The emerging role of proactive therapy in atopic dermatitis and psoriasis

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Abstract

Proactive therapy represents an evolving approach in the long-term management of atopic dermatitis (AD) and psoriasis. Unlike reactive treatment, which targets active symptoms, proactive therapy involves the intermittent, low-dose application of anti-inflammatory agents to previously affected but clinically healed skin to prevent flare-ups. This strategy aims to reduce subclinical inflammation, extend remission periods, and improve patient quality of life. A growing body of evidence supports the efficacy of proactive treatment with topical corticosteroids, calcineurin inhibitors, and vitamin D analogues, demonstrating significant reductions in relapse rates and treatment costs. However, patient adherence remains a key challenge, necessitating structured follow-up and patient education initiatives. This review explores the pathophysiological basis of proactive therapy, its clinical applications, and current evidence supporting its role in AD and psoriasis management. Additionally, we discuss safety

concerns, particularly regarding skin atrophy and hypothalamic-pituitary-adrenal axis suppression and highlight emerging therapeutic options. While proactive therapy has demonstrated a favourable benefit-risk profile, further studies are needed to refine treatment protocols and expand its application to broader patient populations.

Keywords: „proactive therapy"; "maintenance therapy"; "topical treatment"; "atopic dermatitis"; "psoriasis"

Introduction

Proactive therapy is a long-term application of anti-inflammatory therapy to the skin areas previously affected by lesions, which have healed completely, in order to prolong remission period and prevent relapses. In proactive therapy the lowest effective dose is applied to the seemingly unaffected skin twice a week. This approach has been demonstrated to reduce subclinical inflammation, which in turn results in a reduced number of exacerbations, an improvement in quality of life and a reduction in treatment costs.[1] Proactive therapy has been firmly established as a treatment for atopic dermatitis and has been implemented in the management of other inflammatory skin diseases, such as psoriasis[2]. Proactive treatment with corticosteroids, calcineurin inhibitors, and vitamin D analogues is generally well-tolerated and safe. However, a significant challenge is low patient adherence. To enhance treatment compliance, regular follow-up visits or telephonic consultations, along with active patient involvement in therapeutic decision-making, are essential[3,4].

Materials and methods

The aim of this review study is to determine the role of proactive therapy in the treatment of atopic dermatitis and psoriasis. A review of scientific papers with full text was carried out, based on the PubMed database. The keywords used were: 'proactive treatment', 'maintenance therapy', 'atopic dermatitis' and 'psoriasis'. The titles and abstracts were manually screened to assess the relevance of the abstract and the origin of the article. The gathered data were analyzed

and summarized. Since this study was not designed as a meta-analysis, no statistical methods were utilized.

Pathogenesis and clinical manifestation of atopic dermatitis

Atopic dermatitis (AD) is a chronic, recurrent, inflammatory skin disease. It typically manifests in early childhood and tends to diminish in severity with age.[6] The prevalence of the disease is assessed at 15-20% among children and up to 10% among adults. Furthermore, a significant positive correlation was identified in the study "The Global Burden of Atopic Dermatitis" between a country's gross domestic product and disease burden.[7].

The primary symptoms of the disease are eczema, xerosis and pruritus. The disease may present in a variety of ways, but there is a notable correlation between the age of the patient and the observed skin lesions. In infancy, acute lesions with mild erythema are frequently observed on the face, cheeks, and extensor surfaces of the limbs and trunk. However, lesions rarely occur in the nappy area. In children aged over two years, inflammatory lesions are more commonly located on the volar surfaces, with lichenification of the affected areas, chronic eczema, and also with poorly defined pale erythema and dry skin. Adolescents and adults may present with both diffuse and localised lesions on the eyelids, hands, scalp and neck.[8,9].

Atopic dermatitis is a clinically heterogeneous condition. Over the years, numerous diagnostic criteria have been developed to facilitate its identification and management. In 1980, Hanifin and Rajka [7] proposed a set of diagnostic guidelines requiring the presence of at least three out of four major criteria and three out of 23 minor criteria for diagnosis (Table 1).[10] These guidelines remain widely utilized in clinical practice due to their comprehensive characterization of the disease phenotype. Subsequently, additional diagnostic frameworks have been introduced, including the UK Working Party criteria in 1994 and the American Academy of Dermatology (AAD) Guidelines in 2014. The American criteria aim to improve diagnostic accuracy by differentiating atopic dermatitis from phenotypically similar conditions, such as scabies, irritant or allergic contact dermatitis, seborrheic dermatitis, cutaneous T-cell lymphoma, ichthyoses, psoriasis, photosensitive dermatoses, erythrodermas, and immunodeficiency disorders.[11–14]

Minor Criteria	Major Criteria
1. Pruritus 2. Typical morphology and distribution • Flexural lichenification or linearity in adults • Facial and extensor involvement in infants and children 3. Chronic or chronically relapsing dermatitis 4. Personal or family history of atopy, such as asthma, allergic rhinitis, atopic dermatitis	1. Xerosis 2. Ichthyosis/ palmar hyperlinearity/ keratosis pilaris 3. Immediate (type 1) skin test reactivity 4. Elevated serum IgE 5. Early age of onset 6. Tendency toward cutaneous infections (S. aureus and Herpes simplex virus)/impaired, cell-mediated immunity 7. Tendency toward non-specific hand or foot dermatitis 8. Nipple eczema 9. Cheilitis 10. Recurrent conjunctivitis 11. Dennie-Morgan infraorbital fold 12. Keratoconus 13. Anterior subcapsular cataract 14. Orbital darkening 15. Facial pallor/facial erythema 16. Pityriasis alba 17. Anterior neck fold 18. Itch when sweating 19. Intolerance to wool and lipid solvents 20. Perifollicular accentuation 21. Food intolerance 22. Course influenced by environmental/ emotional factors 23. White dermographism/delayed blanch

Table 1 Diagnostic Criteria of atopic dermatitis by Hanifin and Rojka 1980. [10]

The aetiology of the disease is complex and involves a number of factors, including allergic origin, genetics, skin barrier dysfunction and colonization of the skin by microorganisms such as Staphylococcus aureus.[6] Children with parental histories of allergic

conditions are more likely to develop atopic dermatitis (AD). The risk of AD occurrence in offspring is 1.5 times higher when parents have asthma, allergic rhinitis, or food allergies[6,15]. Genome-wide studies have identified 31 distinct chromosomal loci containing susceptibility genes for atopic dermatitis (AD). Among these, the most critical for disease pathogenesis are genes encoding structural and functional epidermal proteins, as well as those regulating innate and adaptive immune responses. Genetic barrier defects reduce the expression of molecules associated with epidermal differentiation and keratinization, such as loricrin, involucrin, and tight junction proteins like claudins and occludins, primarily located in the granular layer of the epidermis. These proteins show an inverse correlation with Th2 biomarkers. Their impairment leads to skin barrier dysfunction, characterized by increased water loss, heightened permeability to allergens and irritants, reduced hydration, and persistent subclinical skin inflammation and pruritus. Subclinical inflammatory lesions and the absorption of food antigens through the skin - whether due to dust contamination or the use of products containing food proteins - can sensitize infants with AD.[6,15,16]

Another significant factor is the altered expression of enzymes involved in the synthesis and processing of free fatty acids and ceramides within the lipid matrix of the stratum corneum. The lipid-rich lamellar granules in the granular layer of the epidermis contribute to a hydrophobic seal. In AD patients, decreased levels of ceramides have been observed. Consequently, the lipid matrix, disrupted by lipid-processing enzymes, becomes a disordered mixture of ceramides, cholesterol, and free fatty acids, with an imbalance among these components. This disruption is thought to result either from increased lipid-processing enzyme activity or from underlying Th2-driven inflammation. Thus, reducing subclinical inflammation through proactive therapy aimed at preventing disease relapses is crucial.[6]

Atopic dermatitis (AD) has been correlated with Staphylococcus aureus colonisation and infection. Indeed, there is a link between microbial communities and inflammatory diseases - the composition and diversity of skin microbiota differ significantly between individuals with eczema and healthy individuals. Atopic skin is characterised by a reduction in commensal bacteria such as Streptococcus, Corynebacterium, Cutibacterium and Proteobacteria and an increase in Staphylococcus species. Interestingly, alterations in the quantity and quality of the skin microbiome may occur prior to the clinical manifestation of disease. Therapeutic interventions - including topical corticosteroids, calcineurin inhibitors, moisturisers and emollients - may help to restore barrier function and normalise the skin microbiome in patients with atopic eczema.[15,17,18]

It has been demonstrated that individuals with atopic dermatitis (AD) exhibit microinflammation even in non-lesional skin. Histological analysis has revealed the presence of a low-grade lymphocytic infiltrate and venule activation in both non-lesional and lesional skin. Moreover, the seemingly healthy skin of patients with AD shows elevated levels of Th2-type inflammatory cytokines and an increased density of high-affinity IgE receptors on the surface of Langerhans cells (LCs) in the epidermis, which play a role in allergen presentation via IgE. Proactive therapy reduces subclinical inflammation and prevents its progression into flare-ups.[19]

Proactive treatment in atopic dermatitis

To reduce ongoing microinflammation and prevent the development of inflammatory lesions, the concept of proactive therapy has been developed. In contrast to reactive therapy, proactive therapy involves the twice-weekly application of topical glucocorticosteroids or calcineurin inhibitors - such as tacrolimus or pimecrolimus - to areas prone to recurrent lesions, in addition to the daily use of emollients after the resolution of acute flares. This approach aims to suppress the progression of microinflammation into clinically evident symptoms.[1]

The first study on proactive therapy was a randomized, placebo-controlled, double-blind, short-term study published in 2002, involving the use of 0.05% fluticasone propionate. At the beginning, patients aged 3 months to 65 years with moderate to severe atopic dermatitis applied the cream daily for four weeks, followed by maintenance therapy—twice weekly for a period of 16 weeks. The study demonstrated that children receiving proactive therapy were 8.1 times less likely to experience flare-ups, while adults were 7.7 times less likely. There were no reports of skin thinning or atrophy with proactive use.[20] Similarly, the first study on proactive therapy with tacrolimus, conducted in 2008[21], showed that over a 12-week period, 56.9% of individuals treated proactively remained in remission compared to 29.6% of those treated reactively. In addition, the median time without an exacerbation was 142 days in the proactive therapy group compared to 15 days in the reactive therapy group.

The benefits of proactive therapy in atopic dermatitis were further confirmed by a meta-analysis published in 2011[2,22]. The meta-analysis conducted by Schmitt encompassed eight randomized controlled trials, including four studies on the topical application of 0.005% fluticasone propionate ointment and 0.05% fluticasone propionate cream, three studies on tacrolimus ointment at a concentration of 0.03% for children and 0.1% for adults, and one study on 0.1% methylprednisolone aceponate cream. The duration of treatment with topical

corticosteroids ranged from 16 to 20 weeks (applied twice weekly), while tacrolimus-based regimens lasted 40 to 52 weeks (applied two to three times weekly). The findings indicated that all proactive approaches were significantly more effective in preventing exacerbations compared to placebo. Moreover, fluticasone propionate appeared to be more effective in maintaining remission than tacrolimus, with 0.05% fluticasone propionate cream showing greater efficacy in preventing atopic eczema flares than 0.005% fluticasone propionate ointment. Furthermore, the meta-analysis by Derek et al. (2023) demonstrated that proactive therapy with tacrolimus, pimecrolimus, and corticosteroids was more effective than reactive therapy in reducing the frequency of disease flares[23].

Studies have also explored the use of proactive therapy with novel agents, such as delgocitinib (a JAK inhibitor). However, to date, no statistically significant superiority of this drug over TCS and TCI has been demonstrated.[2,24]

Proactive therapy with tacrolimus and class II or class III topical glucocorticosteroids has been included in the European Task Force on Atopic Dermatitis (ETFAD) paper for both paediatric and adult patients with disease severity classified as moderate to severe, as determined by a SCORAD score of 25–50, or in cases of recurrent eczema. It is important to note that the baseline of atopic dermatitis management remains daily care with emollients and bath oils[25]. Moreover, the European guidelines permit the use of proactive therapy with TCI and TCS during pregnancy. However, fluticasone propionate should be avoided, as it is the only TCS known not to undergo metabolism by the placenta[26].

Safety

The primary concern associated with proactive therapy utilizing topical corticosteroids (TCS) is the potential for inducing skin atrophy. However, this complication was not identified in the meta-analysis conducted by Schmitt et al.[22] A 2021 evaluator-blinded study assessed the effects of various formulations applied to healthy skin of volunteers in a proactive regimen. The treatments included hydrocortisone acetate 1% cream, methylprednisolone aceponate 0.1% cream, betamethasone valerate 0.1% cream, and an active agent-free base cream, administered once daily twice weekly, as well as pimecrolimus 1% cream, applied twice daily twice weekly. After 12 weeks of application, optical coherence tomography (OCT) identified a reduction in skin thickness exclusively with mometasone furoate. Notably, baseline skin thickness was restored within four weeks after discontinuation. No significant changes in skin thickness were observed with methylprednisolone, hydrocortisone, or pimecrolimus[27].

In the initial study investigating proactive therapy with topical corticosteroids (TCS), 4.5% of children treated with fluticasone demonstrated adrenal suppression, as assessed by biochemical markers.[9,20] However, a meta-analysis conducted by Heickman[28] et al. reported that 2% of children exhibited hypothalamic-pituitary-adrenal (HPA) axis suppression following daily use of low-potency TCS for up to four weeks. The analysis also identified an increasing prevalence of biochemical adrenal insufficiency (AI) in children using moderate-, high-, and very-high-potency TCS, though this difference did not reach statistical significance. Importantly, no clinical manifestations of AI were observed in any of the subjects.

A systematic review of topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) in paediatric patients with atopic dermatitis summarized the potential adverse effects of maintenance therapies[4]. The most common side effects of calcineurin inhibitors are burning and pruritus. No evidence was found to suggest that TCI and TCS use is associated with an increased risk of lymphoma. Additionally, TCIs do not cause skin atrophy, making them particularly well-suited for application on facial skin. The incidence of skin infections among patients using chronic TCI therapy was comparable to that in vehicle-treated patients, occurring in less than 10% of cases in studies lasting over a year. Approximately 20% of patients developed varicella[4].

Pathogenesis and clinical manifestation of psoriasis

Psoriasis is a chronic inflammatory papulosquamous skin disease characterized by a strong genetic predisposition and autoimmune pathogenic mechanisms. Its global prevalence is approximately 2%, though it varies worldwide depending on geographic regions[29–32]. Psoriasis affects men and women equally, with an average age of onset of 33 years. The majority of individuals with psoriasis experience a decline in their quality of life due to the disease, with many reporting a significant negative impact on their psychosocial well-being[30].

The pathogenesis of psoriasis is characterised by the activation of inflammatory pathways in both the innate and adaptive immune cells. A pathogenic triad in psoriasis consists of dendritic cells, TH17 cells, and keratinocytes. Dendritic cells, in particular, have been shown to produce TNF-α and IL-23, which in turn promote T cell differentiation towards the TH17 cell lineage. These TH17 cells then produce the key psoriatic cytokines IL-17, IFN-γ, and IL-22. This process, in turn, leads to the uncontrolled proliferation of keratinocytes, acanthosis, neovascularization, and potent skin infiltration by immune cells. Over 80% of the genes that are upregulated in psoriatic lesions are associated with the activation of keratinocytes and the

infiltration of skin by T cells and macrophages. The result of this activation is skin inflammation[32].

Typical symptoms of the disease are pruritus, burning sensations, and skin tenderness[29]. The most prevalent form of psoriasis is plaque psoriasis (psoriasis vulgaris), which accounts for 80%-90% of cases. The characteristic morphology of this form consists of well-demarcated, salmon-pink plaques with silvery scales. The removal of adherent scales can result in pinpoint bleeding, known as the Auspitz sign. Lesions in plaque psoriasis can range from small erythematous and scaly papules to large, thick plaques, reflecting the dynamic nature of the disease. Plaque psoriasis commonly affects extensor surfaces, including the elbows and knees, trunk, lumbosacral region, and gluteal fold, the scalp, with lesions rarely extending beyond the hairline. Another characteristic feature of active psoriasis is the Koebner phenomenon, in which new psoriatic lesions develop at sites of trauma such as scratching, cuts, or pressure. Patients with moderate to severe psoriasis or during exacerbations may experience significant pruritus, further contributing to disease burden. The outwardly expanding plaque edges and occasional central clearing can lead to an annular appearance, underscoring the dynamic presentation of plaque psoriasis[29,30].

Other variants of psoriasis include inverse psoriasis, guttate psoriasis, pustular psoriasis and erythrodermic Psoriasis. The inverse psoriasis predominantly affects intertriginous regions. Clinically, it is characterized by slightly erosive, erythematous plaques and patches. The guttate psoriasis manifests as an acute eruption of small erythematous plaques. It primarily affects children and adolescents, frequently following group-A streptococcal infections of the tonsils. Approximately one-third of patients with guttate psoriasis progress to plaque psoriasis in adulthood. Pustular psoriasis is distinguished by erythema and multiple sterile pustules that may coalesce[31]. Distinctive subtypes of pustular psoriasis can be distinguished on the basis of anatomical distribution, and these are categorised as follows: generalised pustular psoriasis, which is also referred to as von Zumbusch disease, palmoplantar pustulosis and acrodermatitis continua Hallopeau. Generalized pustular psoriasis presents as an autoinflammatory disorder characterized by recurrent episodes of sterile pustules, fever, and systemic inflammation, which can pose a life-threatening risk. The condition may be precipitated by abrupt discontinuation or rapid dose reduction of systemic or high-potency topical corticosteroids, hypocalcaemia, pregnancy, or infections[30]. Erythrodermic psoriasis is a severe condition in which more than 90% of the body surface becomes erythematous and inflamed. It can arise from any psoriasis subtype and necessitates urgent medical intervention[31].

Proactive therapy in psoriasis

Most patients diagnosed with psoriasis present with a localized form of the disease, typically characterized by mild to moderate severity. Current guidelines recommend topical treatment as the first-line therapy in such cases, including corticosteroids, vitamin D analogs, combined corticosteroid/vitamin D formulations, vitamin A derivatives, anthralin, and newer tar-based preparations. Additionally, the choice of vehicle plays a crucial role in treatment selection, as it can significantly affect both efficacy and potency. The range of available vehicles encompasses creams, lotions, gels, ointments, sprays, powders, and foams[5,33]. Adherence to product labels for steroid-containing medicinal products typically limits their use to a maximum of four weeks of continuous treatment. However, in clinical practice, the duration of therapy is frequently prolonged. Although numerous patients achieve symptom relief during the initial treatment phase, a considerable number later suffer from relapse or worsening of symptoms after discontinuing therapy, as well as tachyphylaxis - a progressively diminished therapeutic response over time[34]. A potential solution for patients may involve the introduction of maintenance therapy, also referred to as proactive therapy, similar to the treatment approach used in atopic dermatitis[35].

In 1991, Katz et al. published the literature report of 'weekend' maintenance therapy, which was a double-blind, placebo-controlled, randomised controlled trial (RCT). Following a 3–4-week course of reactive therapy administered using 0.05% betamethasone dipropionate ointment, patients were instructed to apply the ointment to previously affected skin once a week, with three applications every 12 hours, for a period of 6 months. The disease was in remission in 60% of participants in the active treatment group, compared to 80% relapses in the placebo group. It is noteworthy that no adverse events were observed, particularly with respect to haematology, cutaneous atrophy and HPA axis suppression[2,36]. The maintenance strategy has been demonstrated to be effective in cases of scalp psoriasis. A Poulin et al. study revealed that a once-daily induction with clobetasol propionate shampoo for a period of four weeks, followed by a six-month maintenance phase involving twice-weekly therapy, resulted in a four-month prolongation in time to relapse when compared to a vehicle control.[37]

Several therapeutic strategies have been proposed for the long-term management of psoriasis, including biologic agents, conventional systemic therapies, small molecules, and topical treatments. However, systemic therapies are typically not appropriate for mild disease, which affects the majority of patients with psoriasis. Moreover, topical therapy is associated with fewer adverse effects and lower costs compared to systemic treatments. At present, the

recommended first-line topical therapy for patients suffering from psoriasis is a fixed-dose combination of a corticosteroid (betamethasone dipropionate [BD]) and a vitamin D analogue (calcipotriol [Cal]). This approach is based on high efficacy and a convenient once-daily dosing regimen, which helps to improve patient adherence[5].

In 2021, Lebwohl et al. published the results of the PSO-LONG trial, which comprised an open-label lead-in phase of four weeks, a 52-week randomised, double-blind, vehicle-controlled maintenance phase, and an eight-week follow-up period. The 52-week maintenance period, involving the twice-weekly application of 0.005% calcipotriene and 0.064% betamethasone dipropionate foam, was completed by 251 patients. The vehicle group was administered the Cal/BD foam in a reactive regimen. During the maintenance phase, the estimated median time to first relapse from randomisation was prolonged by 26 days for patients in the proactive group compared with the reactive group. The analysis revealed a 43% reduction in the risk of relapse in the proactive group compared to the reactive group. It is noteworthy that no disparities in serum or urinary calcium levels were observed between the two groups post-treatment. No clinically significant effects on the HPA axis or skin atrophy were noted[38]. Moreover, patients subjected to proactive management exhibited a marked enhancement in their quality of life, as evidenced by a significant increase in DLQI and PSI scores, in comparison to those who received reactive management. This may be due to fewer relapses and longer periods of remission over the course of the year of exposure[39].

The immunological basis of Cal/BD formulation success is as follows: Cal, a vitamin D analogue, exerts its primary action on epidermal dysregulation, leading to a reduction in epidermal hyperproliferation and the promotion of keratinocyte differentiation. In addition to these effects, Cal possesses immunomodulatory properties. Conversely, BD targets pro-inflammatory cytokines and chemokines, while also stimulating keratinocyte differentiation, complementing the action of Cal. Investigations specifically exploring the immunomodulatory properties of Cal/BD have revealed a diminished expansion of Th1 and Th17 cells into psoriatic lesions, indicating a favourable modulation of dendritic cells. Furthermore, the concomitant administration of Cal/BD has been demonstrated to modulate the expression of pro-inflammatory cytokines, including IFN-γ, TNF-α, IL-17 and IL-23, and to upregulate the expression of anti-inflammatory cytokines, such as IL-4 and IL-6.[5]

A matching-adjusted indirect comparison was conducted of long-term efficacy and safety outcomes for calcipotriol/betamethasone dipropionate foam versus halobetasol propionate/tazarotene lotion. The findings of the study demonstrated that the Cal/BD aerosol foam exhibited significantly greater efficacy in both reactive and proactive regimens when

compared with the HP/Taz lotion. Furthermore, the Cal/BD aerosol foam demonstrated a more favourable safety profile than the HP/Taz lotion[40].

Conclusion

Proactive therapy represents a significant advance in the management of both atopic dermatitis (AD) and psoriasis, offering an effective strategy for preventing flares and maintaining long-term remission. Unlike reactive approaches, which focus on treating active symptoms, proactive therapy involves the regular application of topical corticosteroids, calcineurin inhibitors or vitamin D analogues to previously affected areas during remission. Clinical evidence supports its efficacy in reducing relapse rates, prolonging remission periods and improving patients' quality of life. Despite its benefits, safety concerns with long-term corticosteroid use, particularly skin atrophy and hypothalamic-pituitary-adrenal (HPA) axis suppression, require continued evaluation. Current evidence suggests that proactive therapy, when used appropriately, does not significantly increase these risks. Future research should focus on optimising proactive treatment regimens, expanding therapeutic options and evaluating long-term outcomes in different patient populations, including children and pregnant women. In addition, further studies are needed to refine guidelines and establish standardised protocols to ensure widespread implementation of proactive management in dermatological practice and may explore the implementation of proactive therapy in other inflammatory skin conditions.

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