

# Topical corticosteroids versus topical calcineurin inhibitors in atopic dermatitis: A comparative review of efficacy and safety

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## ABSTRACT

**Introduction:** Atopic dermatitis (AD) is a chronic, relapsing inflammatory dermatosis with complex pathogenesis and remains a major challenge in dermatology. Topical therapy constitutes the foundation of treatment across all disease severities. **Objectives:** To compare the clinical efficacy, mechanisms of action, and safety profiles of topical glucocorticosteroids (TCS) and topical calcineurin inhibitors (TCI). **Methods:** A narrative review of the literature, case reports, and international therapeutic guidelines published between 2021 and 2025 concerning the use of TCS and TCI in the treatment of AD was conducted. **Discussion:** TCS are the first-line agents for acute flares but are limited by the risk of skin atrophy with prolonged use. TCIs provide an effective steroid-sparing alternative without inducing epidermal thinning, making them suitable for sensitive areas and long-term therapy. **Conclusions:** TCS and TCI remain central to topical management of AD. Optimal disease control requires proactive, individualized treatment tailored to patient age and lesion localization.

**Key words:** Atopic Dermatitis, Topical Glucocorticosteroids, Calcineurin Inhibitors, Tacrolimus, Proactive Therapy

## INTRODUCTION

Atopic dermatitis (AD), also referred to as atopic eczema, is a chronic, relapsing inflammatory dermatosis characterized by persistent pruritus, xerosis, and eczematous lesions with a typical distribution. It constitutes a central component of the so-called atopic triad and is often the first manifestation of the “atopic march,” preceding the development of other allergic conditions such as allergic rhinitis, food allergy, bronchial asthma or tropical endemic limbo-conjunctivitis [1-3]. Owing to its complex pathogenesis and chronic course, AD represents one of the major challenges in contemporary dermatology and allergology.

Epidemiological data indicate that AD is highly prevalent worldwide, with a marked increasing trend in industrialized countries. The disease affects approximately 10–20% of the pediatric population, with the majority of cases manifesting in early childhood [2,4]. Although historically considered a childhood disease, current evidence demonstrates a substantial prevalence among adults, with reported rates ranging from 2% to as high as 10% [1,4,5]. The clinical significance of AD extends far beyond cutaneous manifestations. According to global burden of disease analyses, AD ranks 15<sup>th</sup> among all noncommunicable diseases and first among skin diseases in terms of disability-adjusted life years (DALYs) [2]. Severe pruritus, the predominant symptom, leads to sleep disturbances,

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anxiety, depression, and reduced productivity at work and school, resulting in considerable socioeconomic costs and a profound deterioration in patients' quality of life [1,5].

The etiopathogenesis of AD is multifactorial and involves complex interactions between genetic predisposition, environmental factors, epidermal barrier dysfunction, and immune dysregulation [2,6,7]. A pivotal role in disease pathophysiology is played by defects of the epidermal barrier, frequently resulting from loss-of-function mutations in the filaggrin (FLG) gene. Filaggrin is essential for proper keratinocyte differentiation and for the formation of the natural moisturizing factor (NMF). Its deficiency leads to increased transepidermal water loss (TEWL), elevated skin pH, and enhanced permeability to allergens and pathogens, consistent with the "outside-to-inside" hypothesis [1,2,6].

Concomitantly with barrier impairment, patients with AD exhibit exaggerated activation of the Th2-dependent immune pathway. Key cytokines, including interleukin-4 (IL-4) and interleukin-13 (IL-13), play a central role in driving inflammation [5,6]. These cytokines not only stimulate IgE production but also downregulate the expression of barrier proteins, such as filaggrin and loricrin, as well as antimicrobial peptides, thereby creating a self-perpetuating pathogenic loop [4,5]. In addition, cytokines such as IL-31 are directly responsible for the induction of pruritus through activation of sensory neurons [5].

An important component of the clinical phenotype is cutaneous microbiome dysbiosis. Patients with AD demonstrate a marked reduction in microbial diversity accompanied by dominance of *Staphylococcus aureus*. Colonization with *S. aureus* occurs in 30% to 100% of patients and correlates with disease severity [1]. Through the production of toxins, superantigens, and biofilm formation, *S. aureus* amplifies type 2 inflammatory responses and further disrupts the epidermal barrier, exacerbating the clinical course of the dermatosis [2,4]. Given this complex pathophysiology, topical corticosteroids and topical calcineurin inhibitors remain the cornerstone of anti-inflammatory therapy, and their comparison in terms of efficacy and safety is essential for the optimization of treatment strategies.

### Significance of Topical Therapy

Topical therapy constitutes the cornerstone of management in atopic dermatitis (AD), playing a

pivotal role in both the treatment of disease flares and long-term maintenance, irrespective of disease severity [8-11]. The primary therapeutic objectives are restoration of the epidermal barrier and reduction of inflammation and pruritus, achieved through regular use of emollients and topical anti-inflammatory medication [10-12]. Despite the emergence of novel topical treatments, such as Janus kinase (JAK) inhibitors and phosphodiesterase-4 (PDE-4) inhibitors, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) have remained the two principal pillars of topical pharmacotherapy for decades [11,13-15]. Current clinical guidelines, including European, Canadian, and Indian consensus statements, consistently identify these drug classes as the standard of care [11,16-18].

### Topical Corticosteroids (TCS)

Topical corticosteroids are first-line agents for the treatment of active cutaneous inflammation in AD [8,10,12].

- Mechanism of action: TCS exert potent anti-inflammatory, antiproliferative, and vasoconstrictive effects. At the molecular level, they bind intracellular glucocorticoid receptors, leading to suppression of proinflammatory cytokine gene transcription and inhibition of phospholipase A2, thereby reducing the synthesis of inflammatory mediators [10,12,15].
- Potency classification: TCS are categorized according to their potency. Different classification systems are used globally, for example a seven-class system in the United States [9,10]. Selection of an appropriate potency depends on patient age, anatomical site (e.g., face versus hands), and disease severity [8,10,11].
- Limitations: Despite high efficacy, prolonged use of TCS is associated with adverse effects, most notably cutaneous atrophy, telangiectasia, striae, and steroid-induced acne [8,16,19]. Additional concerns include tachyphylaxis (decrease of treatment effectiveness in time) and rebound flares following abrupt discontinuation. These risks contribute to so-called steroid phobia, which represents a significant barrier to effective disease control [8,10,19].

### Topical Calcineurin Inhibitors (TCI)

Topical calcineurin inhibitors, tacrolimus and pimecrolimus, represent an important steroid-sparing alternative to TCS [15,19].

- Mechanism of action: TCIs bind intracellular immunophilins (tacrolimus to FKBP-12),

forming a complex that inhibits calcineurin phosphatase activity [19]. This blockade prevents dephosphorylation of nuclear factor of activated T cells (NFAT), thereby inhibiting its nuclear translocation and suppressing transcription of key proinflammatory cytokines, including IL-2, IL-4, IL-5, IFN- $\gamma$ , and TNF- $\alpha$  [15,19].

- Agents: Tacrolimus is available as 0.03% and 0.1% ointment, while pimecrolimus is formulated as a 1% cream. Tacrolimus demonstrates efficacy comparable to mid-potency topical corticosteroids, whereas pimecrolimus is recommended primarily for milder course of disease [10,19].
- Long-term safety: A major advantage of TCIs is the absence of skin atrophy, rendering them suitable for long-term use on sensitive areas such as the face and intertriginous regions [10,19]. Long-term safety has been confirmed in multiple studies. They are recommended not only for adults but also for children. Long time using of tacrolimus is proven to be safe for kids [14,20]. Expert groups, including the Indian STAND AD group, also emphasize the favorable safety profile of TCIs and recommend their use, including off-label application in children under 2 years of age, proving the lack of systemic adverse effects when used appropriately [11].

## Other Topical Treatment Modalities

### PDE4 Inhibitors

Advances in the understanding of atopic dermatitis (AD) pathophysiology have led to the development of novel anti-inflammatory molecules targeting specific molecular pathways. An important class comprises phosphodiesterase-4 (PDE4) inhibitors, which target an enzyme responsible for the degradation of cyclic adenosine monophosphate (cAMP). Increased PDE4 activity in inflammatory cells results in excessive production of proinflammatory cytokines. [9,13]. Crisaborole 2% ointment is a nonsteroidal PDE4 inhibitor approved for the treatment of mild to moderate AD in patients from 3 months of age [6,9]. Clinical trials have demonstrated its efficacy in reducing skin lesions and pruritus, although the therapeutic effect is modest compared with drug vehicle [1,9]. The most common adverse event is application-site pain (burning or stinging), reported in approximately 4–32% of patients [12,13]. Other PDE4 inhibitors under investigation include difamilast, approved in Japan, and roflumilast, which has demonstrated anti-inflammatory efficacy in phase III trials [15,21].

### JAK Inhibitors

Another major therapeutic advance is represented by topical Janus kinase (JAK) inhibitors. The JAK–STAT pathway mediates signaling of multiple cytokines central to AD pathogenesis, including IL-4, IL-13, and IL-31, the latter being directly implicated in pruritus [13,21]. Ruxolitinib 1.5% cream, a JAK1/JAK2 inhibitor, demonstrated rapid pruritus reduction (within 12 hours) and significant improvement in skin lesions in adolescents and adults in phase III TRuE-AD trials [13,15,22]. Delgocitinib, a pan-JAK inhibitor approved in Japan for use in both children and adults, has also shown efficacy in chronic hand eczema [13,21]. Despite their high efficacy, JAK inhibitors carry warnings regarding potential systemic adverse effects; however, the risk appears low with topical administration [15,17,22].

## Emerging Directions: AhR Modulators and the Skin Microbiome

Tapinarof 1% cream is a novel aryl hydrocarbon receptor (AhR) modulator that inhibits STAT6 activation and enhances the expression of epidermal barrier proteins, including filaggrin and loricrin [13,21]. Clinical studies have demonstrated its efficacy in moderate to severe AD in both adults and children. The most frequent side effect event was folliculitis being [13]. In parallel, therapies aimed at modulating the skin microbiome are under investigation, with the goal of reducing *Staphylococcus aureus* colonization and restoring bacterial homeostasis, using strains such as *Roseomonas mucosa* or *Staphylococcus hominis* A9. To date, however, clinical trial results have been inconsistent [9,13].

## Systemic and Adjunctive Therapies

In severe AD refractory to topical treatment, initiation of systemic therapy is required. Conventional immunosuppressive agents, including cyclosporine, methotrexate, and azathioprine, are effective but associated with significant risks during long-term use, such as nephrotoxicity and hypertension [10,12,23]. A major therapeutic breakthrough has been the introduction of biologic agents, notably dupilumab, a monoclonal antibody targeting the IL-4/IL-13 receptor pathway, which demonstrates a favorable efficacy and safety profile, and tralokinumab, an anti-IL-13 antibody [9,12,24]. Oral JAK inhibitors, such as upadacitinib and abrocitinib, represent additional options, offering rapid pruritus relief but requiring laboratory monitoring. Adjunctive treatments

include phototherapy (narrowband UVB), wet-wrap therapy during disease flares, and sodium hypochlorite baths to reduce bacterial superinfection, although their superiority over water alone remains a matter of debate [9,12,22,23].

## MATERIAL AND METHODS

The literature review was conducted using the PubMed, MEDLINE, Scopus, Web of Science, and Google Scholar databases. The search included publications from 2021 to 2025, with particular emphasis on recent clinical studies, systematic reviews, expert guidelines, and consensus documents concerning the use of TCS and TCI in the treatment of atopic dermatitis.

## DISCUSSION

Atopic dermatitis (AD) is one of the most prevalent chronic inflammatory skin diseases, affecting a substantial proportion of both the pediatric and adult populations worldwide [6,10,18]. The complex pathophysiology of AD, involving epidermal barrier dysfunction, immune dysregulation, and environmental and genetic factors, necessitates multidirectional therapeutic strategies [4,23,25]. Despite the emergence of novel targeted therapies, including Janus kinase (JAK) inhibitors and biologic agents such as dupilumab, topical therapy remains the cornerstone of management in mild to moderate disease [12,26,27]. This discussion compares the two principal classes of topical anti-inflammatory agents—topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI)—with respect to their mechanisms of action, clinical efficacy, safety profiles, and practical implications in contemporary dermatology.

### Comparison of the Mechanisms of Action of Topical Corticosteroids and Calcineurin Inhibitors

The fundamental distinction between TCS and TCI lies in their different molecular targets within the inflammatory cascade, which determines both their therapeutic effects and adverse event profiles. Topical corticosteroids, long regarded as the gold standard for the treatment of AD flares, exert broad anti-inflammatory, antiproliferative, and immunosuppressive effects [27,28]. Their mechanism of action involves inhibition of antigen processing and suppression of pro-inflammatory cytokine release

through effects on multiple immune cell types, including T lymphocytes, monocytes, macrophages, and dendritic cells [21,27]. In addition, TCS influence lipid and protein synthesis in the skin, which with prolonged use may result in structural alterations such as epidermal and dermal atrophy [29,30]. Studies by Aschoff et al., using optical coherence tomography (OCT), demonstrated that potent corticosteroids such as betamethasone valerate induce significant epidermal thinning, whereas this effect is not observed with weaker agents used intermittently [29].

Calcineurin inhibitors, including tacrolimus and pimecrolimus, act in a more selective manner. These agents bind to cytosolic immunophilins (FKBP12), forming a complex that inhibits calcineurin phosphatase activity [19]. Inhibition of calcineurin prevents dephosphorylation of the nuclear factor of activated T cells (NFAT) and its translocation to the nucleus, thereby suppressing transcription of genes encoding key pro-inflammatory cytokines, including IL-2, IL-3, IL-4, IL-5, and TNF- $\alpha$  [19,31,32]. Unlike TCS, TCIs do not interfere with collagen synthesis, eliminating the risk of skin atrophy and making them suitable for use in sensitive areas such as the face, neck, and intertriginous regions [27,30,33]. Additional evidence suggests that TCIs may modulate mediator release from mast cells and basophils and reduce Fc $\epsilon$ RI expression on Langerhans cells, further attenuating allergic inflammation [19,32].

Epidermal barrier impairment and pruritus signaling play a central role in AD pathogenesis. Both TCS and TCI may contribute to normalization of filaggrin and loricrin expression, supporting barrier repair; however, TCIs do not adversely affect epidermal lipid synthesis, which is critical for long-term skin integrity [5,30].

### Efficacy of Topical Corticosteroids Versus Calcineurin Inhibitors

Clinical evidence indicates that the efficacy of both drug classes depends on potency and patient population. Comparative studies have shown that tacrolimus 0.1% provides efficacy comparable to mid-potency corticosteroids and superior to weak corticosteroids and pimecrolimus 1% [17,19,30]. A systematic review by Peña et al. confirmed that tacrolimus achieved significantly greater reductions in disease severity, measured by the modified Eczema Area and Severity Index (mEASI), compared with weak TCS in most analyses [30].

In a pediatric study by Mohamed et al., tacrolimus 0.03% ointment was compared with hydrocortisone 1% cream. Although both treatments achieved similar reductions in clinical disease severity, tacrolimus resulted in a significantly greater decrease in serum inflammatory markers, including IL-10, IL-17, and IL-23 [32]. These findings suggest a stronger effect of TCIs on subclinical inflammation, which may be relevant for long-term disease control.

Long-term observational data also support the effectiveness of both approaches. A 3-year study by Perälä et al. in children with moderate to severe AD demonstrated comparable reductions in disease activity with TCS and tacrolimus, with no significant differences in body surface area involvement or EASI scores at study completion [20]. However, direct comparisons between pimecrolimus and tacrolimus consistently show faster onset of action and greater efficacy with tacrolimus, positioning it as the preferred option in more severe disease, while pimecrolimus is generally reserved for milder forms [18,19].

Proactive therapy represents an important strategy in long-term management. Intermittent application of TCS or TCI, typically twice weekly to previously affected areas, effectively reduces relapse rates. Tacrolimus is approved for this indication in many regions, although TCS are commonly used in a similar manner [8,34,35]. Handa et al. demonstrated comparable efficacy of fluticasone and tacrolimus in preventing disease flares, supporting the use of either strategy in maintenance therapy [34].

### Adverse Effects

Safety considerations are central to therapeutic decision-making, particularly in pediatric patients. Despite their high efficacy, TCS are associated with a risk of adverse effects, especially with prolonged use of high-potency formulations. Common local adverse effects include skin atrophy, telangiectasia, striae, and steroid-induced acne [21,27,32]. Using high-frequency ultrasound and OCT, Aschoff et al. confirmed that treatment with betamethasone valerate (a mid-potency corticosteroid) resulted in measurable epidermal thinning within weeks, whereas pimecrolimus did not induce such changes, underscoring the favorable atrophy-related safety profile of TCIs [29].

Concerns also exist regarding systemic effects of TCS absorption, including suppression of the

hypothalamic–pituitary–adrenal axis and potential effects on bone and glucose metabolism. In a randomized study, Gether et al. demonstrated that intensive application of betamethasone ointment over large body surface areas resulted in detectable systemic drug levels and a reduction in markers of bone formation (PINP), suggesting a potential impact on bone homeostasis, although no short-term effect on insulin sensitivity was observed [36]. Conversely, a systematic review by Harvey et al. suggested that intermittent TCS use for up to five years is unlikely to be associated with significant risks of growth impairment or adrenal suppression in children, which is reassuring for clinicians [37].

For TCIs, the most commonly reported adverse effect is a burning or stinging sensation at the application site, particularly during the initial phase of treatment. These symptoms are usually transient and diminish as the skin heals [16,19,32,38,39]. Importantly, TCIs do not cause skin atrophy, making them the preferred option for lesions on the face, eyelids, and skin folds [27,33]. Although the U.S. Food and Drug Administration issued a black box warning regarding a potential risk of malignancy associated with TCI use, extensive long-term studies and meta-analyses have not demonstrated a causal association between topical TCI use and increased risk of lymphoma or skin cancer in humans [16,19,21]. Both European and American dermatologic societies consider TCIs safe when used appropriately [18].

### Long-term Safety

Long-term safety is particularly relevant in AD due to its chronic course. In the 36-month study by Perälä et al., no significant differences in safety outcomes were observed between patients treated with TCS and those treated with tacrolimus, including rates of cutaneous infections and other adverse events [20]. Similarly, the systematic review by Harvey et al. found no increased risk of lymphoma or other malignancies in studies of up to five years' duration in children treated with either TCS or TCIs [37].

Concerns regarding long-term TCS-induced skin thinning can be mitigated by intermittent treatment regimens and avoidance of potent corticosteroids in sensitive areas. Evidence suggests that corticosteroid-induced epidermal atrophy is often reversible upon treatment discontinuation. TCIs, owing to their non-atrophogenic profile, can be safely used on a long-term

basis, as supported by observational studies extending up to 10 years for tacrolimus [28,29].

Nevertheless, vigilance is warranted regarding rare but potential systemic effects. Cohort studies suggest a possible, albeit weak, association between prolonged TCS use and an increased risk of type 2 diabetes or osteoporosis in adults, particularly in those applying potent agents to large body surface areas over extended periods [36,37]. For TCIs, despite the absence of evidence for carcinogenicity in humans, sun protection during treatment is generally recommended [35].

### Practical Implications

Based on the available evidence, the choice between TCS and TCI should be individualized, taking into account patient age, lesion location, disease severity, and patient and caregiver preferences.

According to international guidelines, including Canadian and European recommendations, TCS remain first-line therapy for the management of AD flares due to their rapid onset of action and high efficacy. For lesions on the face, neck, genital area, and skin folds, TCIs (pimecrolimus or tacrolimus) are preferred as first-line agents or as alternatives following a short course of low-potency corticosteroids to minimize the risk of atrophy. These considerations are particularly important in pediatric patients, in whom a higher body surface area-to-weight ratio increases the risk of systemic absorption [11,17,18].

A major challenge in clinical practice is “steroid phobia,” affecting up to 80% of patients and caregivers, leading to poor adherence and suboptimal disease control [28,30]. Patient education regarding the safety of TCS, explanation of fingertip unit (FTU) dosing for accurate application, and reassurance about the low systemic risk with appropriate use are essential for improving adherence [28,35,40]. TCIs provide a valuable alternative for patients reluctant to use corticosteroids, although higher costs may limit access in some healthcare systems [28,30].

Proactive therapy, consisting of twice-weekly application of an anti-inflammatory agent (TCS or TCI) to previously affected skin, is recommended for patients with frequent relapses, as it prolongs remission and reduces overall medication use [11,18,35]. Treatment algorithms proposed by European and Canadian experts emphasize a flexible approach that combines intensive

flare management with long-term maintenance therapy, alongside continuous use of emollients as the foundation of care [11,17,18].

In summary, both TCS and TCI occupy well-established positions in the management of AD. Successful therapy relies on balancing efficacy and safety, tailoring treatment to individual patient characteristics, and providing education to build confidence in the proposed treatment plan. The introduction of newer agents, such as PDE-4 inhibitors and JAK inhibitors, further expands therapeutic options, addressing unmet needs in mild to moderate AD, particularly in cases where conventional therapies are ineffective or poorly tolerated [8,26].

### CONCLUSIONS

Analysis of the available literature allows for clear conclusions regarding the role of topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) in the management of atopic dermatitis (AD). Both drug classes constitute the foundation of topical anti-inflammatory therapy; however, they differ in safety profile, mechanism of action, and preferred sites of application, which determines their use in clinical practice.

Topical corticosteroids remain the first-line treatment for the control of acute disease flares due to their rapid onset of action and high anti-inflammatory and antipruritic efficacy [27]. They are particularly recommended for lesions located on the trunk and extremities, where the skin is thicker. It should be emphasized, however, that prolonged use, especially of high-potency preparations is associated with a risk of clinically significant adverse effects, including skin atrophy, telangiectasia, striae, and, less frequently, systemic suppression of the hypothalamic-pituitary-adrenal axis [10]. Therefore, TCS therapy should be limited to short treatment courses or applied using intermittent regimens [17].

Calcineurin inhibitors (tacrolimus and pimecrolimus) represent a valuable alternative, particularly as steroid-sparing agents. Their key advantage is the absence of atrophogenic potential, which makes them the treatment of choice for lesions located in sensitive areas such as the face, neck, eyelids, and intertriginous regions. Clinical studies confirm that tacrolimus, particularly at a concentration of 0.1%,

demonstrates efficacy comparable to mid-potency topical corticosteroids and superior to pimecrolimus, which is generally recommended for milder forms of the disease [10]. Long-term observational data and meta-analyses have not substantiated earlier concerns regarding an increased risk of malignancy, including lymphoma or skin cancer, associated with TCI use, supporting their safety in chronic therapy [18]. The most commonly reported adverse effect of TCIs is a transient burning sensation at the site of application [10].

Current therapeutic strategies in AD favor a proactive approach, involving long-term intermittent application of anti-inflammatory agents (TCS or TCI), for example twice weekly, to previously affected but clinically healed skin in order to prevent relapses. This strategy has been shown to be more effective than the use of emollients alone. The choice between TCS and TCI should be individualized, taking into account patient age, lesion location, disease severity, and patient preferences, including the frequently encountered phenomenon of steroid phobia, which may adversely affect treatment adherence [10]. Despite the emergence of new therapeutic options, such as phosphodiesterase-4 inhibitors (crisaborole) and Janus kinase inhibitors, TCS and TCI continue to represent the gold standard in the topical treatment of atopic dermatitis [17,22].

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