

The Essential Role of Topical Targeted Therapy in Atopic Dermatitis

Peter Lio MD FAAD,^a Latanya Benjamin MD FAAD,^b Mercedes E. Gonzalez MD FAAD,^c Sophie Guénin MD MSc,^d Adelaide A. Hebert MD FAAD,^e Pearl C Kwong MD FAAD,^f Nanette Silverberg MD FAAD FAAP,^g Lawrence A. Schachner MD FAAD FAAP^h

^aDermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL

^bYoung Skin MD, Coral Springs, FL

^cPediatric Skin Research, Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL

^dDepartment of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY

^eDepartment of Dermatology and Pediatrics, McGovern Medical School, and Children's Memorial Hermann Hospital, Houston, TX

^fSuncoast Skin Solutions Inc., Apex Clinical Trials, Jacksonville, FL

^gDepartment of Pediatric and Adolescent Dermatology, Icahn School of Medicine at Mount Sinai, NY, NY

^hDermatology and Pediatrics, Pediatric Dermatology, University of Miami School of Medicine, Miami, FL

ABSTRACT

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disorder marked by immune dysregulation, epidermal barrier dysfunction, microbiome imbalance, pruritus, and xerosis. Despite therapeutic advances, topical treatments remain the foundation of AD management across all severities. However, most existing topicals address only limited aspects of the disease such as itch or inflammation, resulting in frequent relapse and patient dissatisfaction.

Methods: A focused literature review of topical AD therapies published between January 2015 and July 2025 was conducted, emphasizing efficacy and safety. Recent findings were synthesized in this narrative review to highlight the ongoing role of topical treatments in AD management.

Results: AD is a multifactorial condition influenced by *Staphylococcus aureus* colonization, immune dysregulation, genetic susceptibility, and environmental factors. These contribute to disease pathogenesis, the itch-scratch cycle, and barrier disruption. While systemic therapies are important, AD treatment continues to rely heavily on topical agents. Optimal management should target inflammation, restore barrier function, and address microbiome dysbiosis. Most current treatments focus on individual disease components, with few addressing the full pathogenic spectrum. Emerging evidence on zabalafin (9.5%) hydrogel, a novel botanical topical therapy, suggests potential multi-target benefits, including anti-inflammatory, antipruritic, antimicrobial, and anti-xerotic effects.

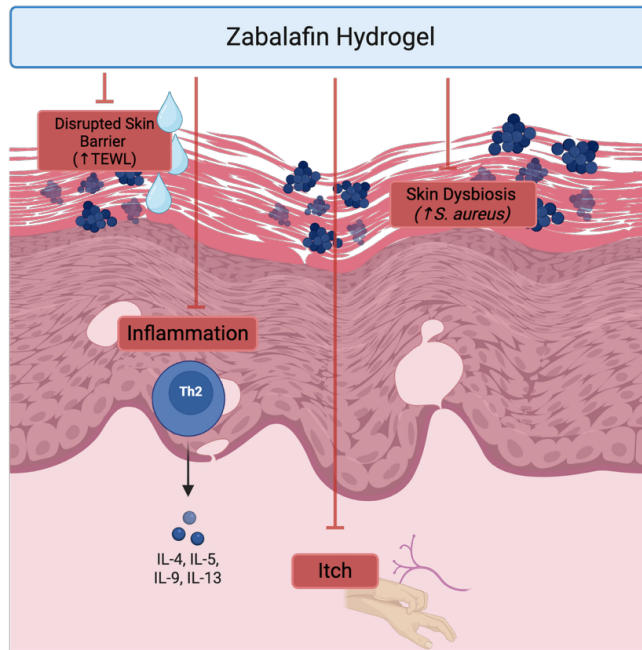
Conclusion: There remains a significant unmet need for topical therapies that comprehensively address the AD continuum, including inflammation, itch, barrier dysfunction, and microbial imbalance. Novel agents such as zabalafin may help bridge this gap.

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INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease with a relapsing and remitting course over a patient's lifetime.^{1,2} This chronic skin condition is estimated to affect up to 20% of children and 1% to 6% of adults worldwide.³ AD is a heavily heterogeneous spectrum of disease affecting all age groups and skin types with varied clinical presentation and severity. The disease exists on a continuum with 4 significant skin findings: inflammation, dysbiosis/colonization/infection, pruritus, and xerosis, termed the "4 demons".⁴

Clinically, AD presents with recurrent, erythematous, pruritic eczematous plaques accompanied by dry, sensitive skin. AD frequently begins in infancy or early childhood and affects over 30 million people in the United States. The prevalence of this widespread disease is associated with an estimated global economic cost of \$5 billion annually.⁵ In addition, AD is associated with increased stress, low self-esteem, poor sleep, and overall decreased quality of life.⁶

FIGURE 1. Zabalafin hydrogel mechanism of action.

Zabalafin targets all aspects of the atopic dermatitis continuum by addressing skin dysbiosis, inflammatory dysregulation, xerosis, and itch.

AD has a complex pathophysiology involving immune dysregulation, genetic predisposition, environmental factors, *Staphylococcus aureus* colonization, and skin dysbiosis, all of which contribute to intense pruritus and a compromised skin barrier.⁴ There has been extensive scientific debate regarding whether AD is primarily driven by epidermal barrier dysfunction (“outside-in”) leading to antigen penetration and subsequent immune activation, or by inherent immune dysregulation (“inside-out”), in which aberrant T helper cell (Th) 2 cell activation results in barrier dysfunction and disease progression.⁴ Regardless of the inciting factor, successful treatment should target as many pathogenic factors as possible.

This treatment paradigm starts with topical therapies that provide local, skin-specific therapy while offering symptomatic relief.⁷ Topical therapy is the essential foundation of AD disease management. Topicals treat the disease directly at the site and provide patients with rapid symptomatic relief. Currently available topicals may be divided into 4 categories: (1) moisturizers and emollients, (2) topical corticosteroids (TCS), (3) topical calcineurin inhibitors (TCI), and (4) topical nonsteroidal agents such as PDE4 inhibitors (crisaborole, roflumilast), JAK inhibitors (delgocitinib [only approved for hand eczema], ruxolitinib), and aryl hydrocarbon receptor agonist (tapinarof).⁶ Most of these agents target the diseased skin barrier by reducing inflammation and helping restore

skin hydration; however, none addresses all 4 aspects of AD pathology: inflammation, *S. aureus* bacteria, pruritus, and xerosis.⁸

Here, we present evidence from a literature review highlighting the critical role of topical therapies in addressing the AD disease trajectory. We also introduce zabalafin hydrogel, a novel botanical topical treatment that addresses all aspects of AD pathogenesis, unlike any existing singular topical agent.

MATERIALS AND METHODS

Literature Review

The authors reviewed the most recent literature on the efficacy and safety profiles of topical therapy for maintaining control of the AD continuum, focusing on 3 main topics: (1) place in therapy of topicals (2) effectiveness and safety of topicals, and (3) different approaches to the management of patients treated with topicals in a real-world clinical setting.

Two authors (AA and SG) conducted a structured literature review on AD triggers and current best practices in topical AD treatment, searching PubMed and Google Scholar with the following search terms: *AD triggers AND skin dysbiosis OR staphylococcus aureus-driven colonization OR infection OR immunological OR genetic OR environmental OR inflammation.*

AD flares AND topical treatment OR topical corticosteroids OR topical calcineurin inhibitors OR PDE-4 I OR Zabalafin OR topical antimicrobial OR antimicrobial resistance OR topical antibiotic OR topical antibiotic resistance OR cyclosporine OR interleukin (IL)-4/13 inhibitors OR IL-13 inhibitors OR JAK inhibitors.

Excluded were publications in languages other than English, not including topicals for AD. The review process involved examining titles and abstracts, followed by full articles. Selected articles included clinical guidelines, algorithms, consensus papers, systematic literature reviews, and clinical studies published in English from January 2015 to July 2025. Selected publications were manually reviewed, with any discrepancies resolved through discussion. This process yielded 34 articles that qualified for inclusion and were deemed clinically relevant to inform the crucial role of topical treatment for the AD continuum.

SAIGE (*S. aureus*, Immune Dysregulation, Genetic Predisposition, Environmental Influence) Triggers

The pathogenesis of AD is multifactorial and driven by complex interactions among triggers, including *S. aureus* colonization and infection, immune dysregulation, genetic predisposition, and environmental factors. Taken together, these triggers are termed the SAIGE triggers.⁴ SAIGE triggers are uniquely intertwined and together contribute to disease onset and exacerbations. For example, skin microbiome dysbiosis and *S. aureus* overgrowth are characteristic of lesional AD skin. This dysbiosis and *S. aureus* colonization are thought to be primary drivers of inflammation, itch, and subsequent skin barrier disruption in AD.⁴

Deng et al demonstrate that *S. aureus* directly activates pruriceptor sensory neurons that drive itch and lead to the itch-scratch cycle and subsequent scratch-induced skin damage.⁹ Further studies have found that other bacteria, including *Corynebacterium mastitidis* and *Corynebacterium bovis*, are present at the onset of AD. *C. bovis* was shown to be primarily responsible for driving a robust Th2 cell response, while *S. aureus* potentiated these signals to AD manifestation.¹⁰

Clinically, patients with mild dysbiosis may present with mild inflammation or flares, whilst those with *S. aureus* overabundance will present with moderate to severe AD. Further, the proportion of *S. aureus* has been shown to be higher during disease flares, suggesting that AD treatments that reduce *S. aureus* populations and restore skin microbial diversity would be most effective.¹¹ Remaining SAIGE factors, such as environmental season changes, genetic predisposition, or existing immune dysregulation, may also significantly contribute to determining in which way the *S. aureus*-driven AD pendulum will swing.^{4,12}

Essential Role of Topical Therapy in Atopic Dermatitis Management

Topical therapy is the key component of real-world AD treatment. This is evidenced by pivotal AD clinical trials such as Liberty Ad Chronos, which investigated dupilumab in conjunction with TCS and TCI therapy, highlighting the essential and ubiquitous use of topical therapy in AD.^{13,14} These study designs reinforce the vital role that topicals play in the management of AD regardless of concomitant systemic therapies.

Effective management of AD begins with topical therapy aimed at repairing the defective skin barrier. Moisturizers are the foundation of optimal AD treatment, regardless of disease severity. They reinforce the damaged epidermal barrier, which is associated with increased transepidermal water loss (TEWL) and enhanced penetration of foreign antigens.¹⁵ In addition, AD-affected skin has been linked to filaggrin deficiency and reduced levels of key epidermal lipids such as ceramides, fatty acids, triglycerides, and cholesterol, which are critical for maintaining barrier integrity.¹⁵ Consequently, moisturizers, emollients, and humectants may help restore this weakened barrier by providing exogenous lipids, lubricating the skin, reducing TEWL, and improving skin hydration.¹⁵ Daily moisturizer use has been shown to improve AD and is postulated to prevent or delay AD onset in infants.^{16,17}

For patients who are uncontrolled with gentle skincare and moisturizers alone, TCS is often considered the first-line therapy in AD. TCS functions by broadly reducing inflammation and itch in the skin. Whilst effective, TCS are not appropriate for long-term use and may harbor unwanted cutaneous and systemic side effects such as skin atrophy, hypopigmentation, telangiectasias, and hypothalamic-pituitary-adrenal (HPA) axis suppression, particularly in children or patients with a large affected body surface area (BSA).⁸ In addition, there is increasing concern of TCS withdrawal syndrome among patients and parents, which is described as worsening skin inflammation upon cessation of steroid use.⁶ Taken together, the adverse effect profile of TCS has made many patients cautious of their use, with an increasing number of patients becoming “steroidphobic,” which ultimately leads to under-treatment and poor treatment compliance.⁶

Corticosteroid alternatives, such as topical calcineurin inhibitors, topical JAK inhibitors, topical PDE-4 inhibitors, and topical aryl-hydrocarbon receptor agonists, are increasingly used in AD treatment, harboring fewer side effects than TCS. These alternatives are more appropriate for long-term use and have been shown to reduce AD exacerbations.^{6,18} Despite their effectiveness, these topical treatments primarily target the inflammatory component of itch.

Unmet Need for Topicals in Atopic Dermatitis + Zabalafin Hydrogel

While significant advancements have been made in the field of AD, there remains a critical unmet therapeutic need for a topical therapy that targets the 4 main components of AD pathogenesis. Topicals play an overwhelmingly large role in the treatment landscape of AD. In an online survey of 2,005 patients, topical therapies were the most frequently reported modality of treatment: 85% of participants reported topical use, and 46% reported prescription topical medications.¹⁹ Over 80% of survey participants reported having used or currently using an over-the-counter (OTC) topical, and 76% of survey participants reported having used or currently using a prescription topical. This highlights the widespread prevalence of topical therapy use and how vital it is for AD therapy.

Interestingly, despite this high rate of topical use, most patients reported high dissatisfaction with current topical therapies.¹⁹ Thus, there exists a significant unmet need for an effective and safe topical AD agent that treats the entire AD disease continuum via a direct, multi-target approach to increase patients' response and satisfaction.

Zabalafin hydrogel is a novel, first-in-class topical agent with anti-inflammatory, anti-pruritic, anti-xerosis, and *S. aureus* modulating effects for the treatment of AD.²⁰ Zabalafin hydrogel is a topical botanical drug containing multiple bioactive compounds that target all aspects of the AD continuum. Application of the hydrogel forms a "liquid bandage" over the AD lesion, mimicking the effect of localized wet wraps on the skin. The zabalafin hydrogel barrier helps to restore microbiome balance and skin barrier function.

A randomized, double-blind, vehicle-controlled phase 2a clinical trial evaluated the safety and efficacy of zabalafin (9.5%) hydrogel in treating AD in adults and children with AD aged >2 years (n=41) over a 4-week period. The hydrogel was applied twice daily in patients with mild to moderate AD without secondary infection, as well as in those with mild to moderate AD and secondary infection.²⁰ By week 4, over 50% of study participants achieved an EASI 75, demonstrating that the novel topical was effective in treating the inflammatory component of AD.²¹ In addition, in an open-label study in infected AD patients, zabalafin hydrogel was effective in treating the bacterial component of AD, demonstrating a significant reduction in bacterial infection and colonization over a 12-week period, as well as reducing or clearing the AD.^{20,21} In patients with *S. aureus* infection, 84% cleared at weeks 8 or 12, with 100% of patients with MRSA being cleared. This demonstrates the potential of zabalafin to reduce *S. aureus* levels, which, in turn, can potentially modify the disease trajectory by decreasing AD flares, which are known to be preceded by a rise in *S. aureus*

levels.¹¹ Lastly, zabalafin was effective in treating itch, with 80% of patients achieving an NRS improvement of >4 at week 8 and 100% reporting improved quality of life.²¹ Zabalafin hydrogel has a favorable safety profile with no significant safety signals observed; only one patient during the phase 2a trials had mild transient stinging at the application site, which did not interrupt treatment.²⁰

Results demonstrate that zabalafin hydrogel effectively targets AD inflammation and itch while conferring antimicrobial properties. With concerns of growing antibacterial resistance, zabalafin offers a botanical alternative with broad-spectrum antibacterial activity, with little potential for antibacterial resistance, and good activity against MRSA.¹² To summarize, zabalafin hydrogel is a comprehensive, effective, and safe topical agent that addresses the full spectrum of the AD continuum in a wide variety of AD patient ages and presentations.²⁰ Zabalafin disrupts bacterial replication, inhibits the AD inflammatory cascade, and attenuates pruritic mechanisms while moisturizing the skin and restoring the skin barrier, and reduces *S. aureus* levels (Figure 1).¹²

Topical Therapy in an Eczema Action Plan

The mainstay of therapy for all AD patients is topicals. Topicals are constantly used at all stages of AD, from mild to severe, and should be used in combination with systemic agents to help patients get clear and stay clear from AD.⁶ These topical agents can become especially helpful when addressing flares while on systemic options, as they work rapidly to relieve patients of their symptoms. Many patients and physicians will partner to develop personalized eczema action plans for potential flares. These plans typically include the use of a TCS, moisturizer, and gentle cleanser for up to one week to treat flares. A maintenance regimen of topical non-steroidal may follow this to maintain AD "hot spots" clear, accompanied by moisturizers and a gentle cleanser.⁶

However, the drawback to the topicals proposed in this plan is that TCS and most non-steroidal topicals only address the inflammatory aspect of the AD continuum. Ideally, a topical would address all aspects of AD pathogenesis to help achieve and maintain control of AD flares. Zabalafin hydrogel targets all 4 AD demons and provides the antimicrobial activity required to break the cycle of *S. aureus*-triggered AD flares. As a safe, gentle, and pain-free efficacious botanical product, zabalafin does not harbor the unfavorable side effect profile of TCS, which may make it more appealing to steroid-phobic individuals or for the pediatric population. Taken together, zabalafin is an essential addition to the topical AD armamentarium as it is the only topical to date that targets all aspects of the AD continuum effectively and safely.

CONCLUSION

Topical therapy is an essential pillar of AD treatment and management. Most AD patients will use a topical treatment at some point in their lifetime. Therefore, effective and safe topicals for the greater AD-affected population are vital. AD is a complex, highly heterogeneous disease that is largely understood to be triggered and exacerbated by SAIGE factors. To date, most topical and systemic therapies have primarily focused on immune dysregulation associated with AD flares. Currently available topicals, such as TCS, address AD inflammation but do not directly address skin microbiome dysbiosis and xerosis. Zabalafin (9.5%) hydrogel was found to be the only topical that synchronously addresses the full spectrum of the AD continuum at the skin. In addition, the botanical anti-microbial activity of the novel topical introduces disease-modifying potential by reducing pathogenic *S. aureus*, including MRSA, population in the skin microbiome.

DISCLOSURES

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AUTHOR CORRESPONDENCE**Sophie Guénin MD MSc**

E-mail:..... Sophiehelene.guenin@gmail.com