Clinics in Dermatology (2017) **35**, 375–382

ELSEVIER

Clinics in Dermatology

Current and emerging topical therapies for atopic dermatitis

Jeremy Udkoff, MA, Andrea Waldman, MD, Jusleen Ahluwalia, MD, Jenna Borok, BS, Lawrence F. Eichenfield, MD*

[a]*Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, 8010 Frost Street, Suite 602, San Diego, CA 92123*
[b]*Departments of Dermatology and Pediatrics, University of California, San Diego School of Medicine, 9500 Gillman Drive, La Jolla, CA 92093*

Abstract The pathogenesis of atopic dermatitis (AD) involves epidermal barrier dysfunction and T helper cell type 2 (T_H2) lymphocyte-driven inflammation. Cytokines, such as interleukin 4 (IL-4) and IL-13, are important in this reaction. They stimulate B cells to produce immunoglobulin E, causing atopic disease. This process has been well characterized, and new therapies for AD, such as phosphodiesterase 4 (PDE-4) inhibitors, T_H2-expressed chemoattractant receptor–homologous molecule antagonists, and Janus kinase inhibitors, work by antagonizing this cellular pathway. Recently, there have been many advances in treatment strategies and novel therapies for AD. This review summarizes the clinical evidence supporting the use of current and emerging topical treatments for AD, as well as their safety and efficacy profiles. Crisaborole, a novel PDE-4 inhibitor, is of particular note because phase III clinical trials were recently completed, as summarized here. It is prudent for dermatologists to be current with updates in the field because therapies are constantly changing. In addition to the academic interest, this results in improvement of patient care and advancement of the field.

Introduction

Atopic dermatitis (AD) is the most common inflammatory dermatologic disease worldwide.[1] It has an estimated global prevalence of 15-30% in children and up to 10% in adults, with 229,761,000 reported cases in 2010.[1–5] The clinical presentation of AD varies depending on the age and race of the patient. Morphologically, AD classically presents with erythema, excoriation, lichenification, papulation, oozing, and crusting.[2] Individuals with darker skin may present with lichenoid papules, follicular accentuation, pigmentary changes, and/or xerosis.[2] AD has been termed "the itch that rashes," because pruritus is a hallmark of AD, often resulting in characteristic excoriations, increased inflammation, and worsening of the disease.[5–7] Pruritus can be more intense in the evening and may contribute to the disrupted sleep that occurs in those with AD.[8] This represents a treatment opportunity, and aside from lessening signs of AD, many treatments, such as topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and emollients, may play a role in reducing pruritus.[6] AD is associated with an increased prevalence of comorbidities, such as skin infections, immunoglobulin E (IgE)–mediated diseases (atopy), and mental health disorders.[9,10]

* Corresponding author. 8010 Frost Street, Ste 602, San Diego, CA 92123.
E-mail address: Leichenfield@rchsd.org (L.F. Eichenfield).

http://dx.doi.org/10.1016/j.clindermatol.2017.03.010
0738-081X/

The pathogenesis of AD is complex, involving aspects of epidermal barrier dysfunction and cutaneous inflammation. Transepidermal water loss (TEWL) is a proxy for measuring biophysical defects within the skin barrier. In infants, it has been found to be a strong predictor for developing AD later in life.[11] The inflammation in AD is markedly influenced by T helper cell type 2 (T_H2)–driven inflammation, with a broad set of cytokines. Studies have evaluated the impact of inflammatory mediators on AD skin lesions, as well as their influence on barrier function and B-cell–mediated immunoglobulin production. The recognition of phosphodiesterase 4 (PDE-4) as influencing inflammation in circulating inflammatory cells in AD has been investigated and set as a target for new topical therapies. In addition, other immunologic targets include Janus kinase inhibitors and T_H2-expressed chemoattractant receptor–homologous molecule (CRTH2) antagonists. Theses cytokines may also serve as a driving force in the development of other atopic diseases, including IgE-mediated food allergies, asthma, and allergic rhinitis.[2] Accordingly, understanding the pathogenesis of AD is crucial in the development of effective therapies and the control of AD. Topical therapies are currently the cornerstone of AD therapy. This likely is due to their limited systemic absorption, focused local effects, and low cost. Topical PDE-4 inhibitors are under investigation, with crisaborole having recently completely phase III clinical trials. Over the past 20 years, medications with novel mechanisms have been developed and treatment paradigms have shifted to include early, proactive therapy.

Treatment paradigms

Early therapy

Epidermal barrier dysfunction, characterized by increased TEWL, is thought to play a large role in the allergic sensitization to protein antigens and progression of AD.[12] Early interventions to repair this epidermal barrier may be useful in delaying the progression of disease. The Barrier Enhancement for Eczema Prevention study was created to determine the feasibility of early prophylactic use of emollients in high-risk patients. Infants younger than 3 weeks of age were recruited. The group reported a large reduction in AD development in the emollient group at 6 months of age with no differences in adverse events between the emollient and untreated groups.[13] A similar Japanese study found that neonates who received daily moisturizer during the first 32 weeks of life were 32% less likely to develop AD or eczema compared with no intervention.[14] Larger trials in the United States and United Kingdom are underway to further characterize this effect and to determine optimal timing and regimen, because the prospect of primary prevention for AD is novel and of the utmost importance. A more in-depth review of currently available data on early emollient introduction can be found in Part II of this series.

Long-term treatment strategies and safety profiles

AD is a chronic condition that follows a remitting and relapsing course usually characterized by disease flares between periods of quiescence. The strategy for prolonging quiescent periods is dependent on the patient and disease severity. In two prospective studies, daily moisturizing lengthened the time until an AD flare compared with no treatment.[15,16] This approach may significantly improve the overall course of AD in some patients, but others may have relapsing disease that requires a stronger intervention.

Proactive therapy has gained popularity in the treatment of relapsing AD. A systematic review and meta-analysis of randomized control trials (RCTs) found the application of TCS or TCI to commonly affected but inactive areas two to three times weekly to be more effective in controlling AD flares than vehicle.[17] The analysis included eight RCTs: five RCTs with twice weekly application of fluticasone propionate or methylprednisolone aceponate (TCS) for 16 to 20 weeks and three RCTs using 0.3% (children) to 1% (adults) tacrolimus (TCI) ointment two to three times weekly for 40 to 52 weeks. Aside from indicating TCS's and TCI's superiority to vehicle, indirect evidence from these trials found TCS to be superior to TCI as measured by relative risk of a disease flare. Another prospective vehicle control study found daily topical pimecrolimus to be effective in decreasing flares and reducing or eliminating the need for the acute use of TCS.[18]

The long-term safety of TCI and TCS has been well studied. A randomized, open-label trial comparing pimecrolimus (with TCS for breakthrough flares) and mild- or moderate-potency TCS recruited 2418 infants with mild to moderate AD (Investigator's Global Assessment [IGA] score of 2 or 3) between 3 and 12 months old (off-label use in the United States).[19] Patients were monitored for 5 years to compare the safety of these treatments and characterize their long-term effectiveness. Treatment success was defined as an IGA score of 1 (clear) or 2 (almost clear). At completion of the study, both groups had greater than 85% treatment success overall and 95% had facial success. Both groups had similar safety outcomes. Humoral immune function was measured with immunoglobulin titers and $CD19^+$ cell count, and cellular immunity was measured with $CD3^+$, $CD4^+$, $CD8^+$, CD45 RA^+, and CD45 $R0^+$ cell counts in addition to *Candida* skin testing and $CD3^+$ T-cell function assays. This wide array of immunologic tests indicated no differences between the two treatment groups and a historical control group.

Prolonged and excessive use of potent TCS may contribute to the development of striae, short-term hypothalamic-pituitary-adrenal axis alteration, and ophthalmologic disease[20]; scheduled use of intermittent TCS has not been found to cause skin atrophy, but multiple studies reported a slightly higher rate of systemic infections.[21] Overall the risk-to-benefit ratio of proactive, long-term, scheduled, intermittent steroids is acceptable, and a recent consensus conference on AD concluded that areas of frequent relapsing AD should be treated with the application of TCS twice per week.[22] Based