



Current and emerging topical therapies for atopic dermatitis

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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.

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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}

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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. These 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 completed 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 disease²⁰; 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

on the current body of evidence, they recommended 15 g in infants, 30 g in children, and 60 to 90 g in adolescents or adults as safe monthly doses of medium- to high-potency TCS.

The US Food and Drug Administration (FDA) requires rigorous testing for efficacy and safety before it approves medications for general use. Emerging treatments, such as PDE-4 inhibitors, must undergo significant testing in phase II studies, including pharmacokinetic studies in different age classifications, as well as large phase III vehicle- or placebo-controlled studies before approval. Long-term studies take approximately 1 year before drug approval, and extended clinical experience is important in assessing more long-term safety profiles, including postmarketing surveillance.

In 2006, the FDA required the inclusion of a boxed warning label cautioning against the theoretical risk of TCI-associated malignancy.²³ Subsequent to this mandate, two longitudinal registries (A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety [APPLE] and Pediatric Eczema Elective Registry [PEER]) were initiated to monitor the incidence of malignancy in patients using TCI therapy. The interim data from the APPLE registry are expected in the first quarter of 2017, and the PEER registry will continue to collect data through 2017. Despite the FDA's required labeling, epidemiologic analysis of data from the Health Improvement Network Database in the United Kingdom did not detect an increased risk for malignancy with TCI use.²⁴ A recent meta-analysis found an association between AD and developing lymphoma with a risk ratio of 1.43 (95% confidence interval [CI], 1.12-1.81) and a positive correlation with AD severity.²⁵ Tacrolimus or pimecrolimus use had no significant association with lymphoma risk. Of note, high-potency TCS use was associated with an increased lymphoma risk in case-control studies with an odds ratio of 1.73 (95% CI, 1.52-1.97); however, low-potency steroids were not found to have a significant association. Additional published information on the clinical and epidemiologic studies surrounding TCI use and malignancy noted no increased risk.²³ Finally, a systematic review of the literature by the same group included multiple tacrolimus trials and more than 5800 patients and noted no cases of lymphoma.²⁶

Despite the lack of evidence supporting malignancy risk from TCI, many clinicians have discontinued use of TCI based on the FDA labelling. Many patients who previously achieved control of AD with TCI discontinued therapy and have recalcitrant disease, particularly in the face and intertriginous areas, because TCS cannot be used on a prolonged basis to control this manifestation of disease.

Commonly used topical therapies

Topical corticosteroids and topical calcineurin inhibitors have been used in the treatment of AD for decades. They are well-studied treatments with much evidence to support their tolerability and efficacy.

Topical corticosteroids

The effectiveness of TCS in the treatment of AD has been reported by more than 110 RCTs.²⁷ TCS are recommended for active AD lesions, chronic cutaneous manifestations (ie, lichenification), and the symptomatic management of pruritus.^{28,29} A recent consensus conference concluded that TCS should be applied nightly during acute flares of disease.²² Many providers prefer short bursts of high-potency TCS and subsequent taper. Others recommend a long course of lower-potency steroids with gradual increase in potency according to patient tolerance and response. Short bursts of potent TCS may be advised in children with moderate to severe disease, despite children's increased systemic absorption and surface area-to-weight ratio.³⁰

The unfortunate reality is that TCS are stigmatized, and patient education is necessary to reduce steroid phobia.³¹ In fact, one group performed a survey of dermatology outpatients and their parents and found 24% admitted noncompliance due to concerns surrounding TCS adverse effects.³² Patients' most frequent causes for concern were skin thinning in 34.5% and the risk for systemic absorption leading to delayed growth and development in 9.5%. A more recent cross-sectional study noted similar results, with nonadherence in 28.3% of patients due to TCS concerns.³³ The study also noted a significant decrease in patient concerns after educational intervention. As a result, patient education to address such fears is crucial to ensure patient compliance in the treatment of AD.³⁴

Topical calcineurin inhibitors

TCI are second-line agents for treating AD that act on T cells and decrease the expression of inflammatory cytokines, such as IL-3, interferon γ , tumor necrosis factor α , and granulocyte-macrophage colony-stimulating factor, that would otherwise contribute to cutaneous inflammation.³⁵ Pimecrolimus (Elidel) cream in 1% strength and tacrolimus ointment (Protopic or generic by Glenmark Pharmaceuticals Ltd) in strengths from 0.03% to 0.3% are the available topical TCI for use in AD. Tacrolimus is FDA approved for moderate to severe AD, pimecrolimus for mild to moderate AD. Short- and long-term clinical trials have reported superior effectiveness of these agents in reducing AD severity and reversing skin atrophy over vehicle.³⁶⁻³⁹ Although both agents lessen the body surface area affected by AD and improve patient evaluation of disease severity, two 6-week comparative studies found a greater positive effect with tacrolimus therapy.^{40,41}

TCI are particularly useful in treating sensitive sites such as the face and intertriginous areas, because they do not cause cutaneous atrophy.^{42,43} Severe side effects to TCI are rare; however, burning or stinging occasionally occurs during the first few applications. A short course of TCS started just before TCI treatment may be used for symptomatic relief.⁴⁴

A consensus review on TCI safety espoused their safety and efficacy in infants with AD as young as 3 months of

age.⁴⁵ Unfortunately, regulatory bodies in the United States and Europe restrict TCI use to patients 2 years and older.

What's on the horizon?

Many new topical therapies are currently being developed. This section is not an exhaustive review but rather discusses agents with recently published results from phase II or phase III clinical trials.

PDE-4 inhibitors

Phosphodiesterase is an intracellular enzyme that inactivates cyclic adenosine monophosphate (cAMP), an intracellular signaling molecule. In 1996, a study reported increased PDE activity with subsequently decreased intracellular cAMP levels in peripheral leukocytes of patients with AD. The researchers also found that the introduction of an *in vitro* PDE-4 inhibitor reduced levels of proinflammatory cytokines, such as IL-4, produced by T_H2 cells.⁴⁶ These data support our current understanding of PDE-4 inhibitors, which downregulate the inflammatory response within leukocytes by suppressing various interleukins, interferon γ , and tumor necrosis factor α .⁴⁷ More specifically, reduced T_H2-derived IL-4, IL-5, and IL-13 cause decreased production of IgE, thereby halting the pathogenesis and disease progression of AD⁴⁸; thus, PDE-4 inhibitors decrease proinflammatory cytokines and block the sequence of inflammatory events underlying AD.

There are 11 families of PDE enzymes and each displays different selectivity. PDE-4 selectively inactivates cAMP, whereas PDE-2 may inactivate cAMP or cyclic guanosine monophosphate.⁴⁹ Manufacturers have claimed that the selectivity of different PDE-4 inhibitor may influence efficacy of such products; however, more data are needed to clarify these effects.

Crisaborole

PDE-4 inhibitors in the form of topical or systemic treatments have been recently approved, and others are currently under investigation. Crisaborole (Anacor Pharmaceuticals, Inc.), previously known as AN2728, is a topical PDE-4 inhibitor with a lightweight structure and novel architecture that is boron-based to allow for deeper skin penetration and molecular stabilization.⁵⁰ The positive safety profile of crisaborole was reported in AD patients 2 years and older in one phase Ib trial, which also found limited systemic absorption of the drug, and two phase II clinical trials by monitoring laboratory values and adverse events.^{51–53} One phase IIa clinical trial⁵¹ reported a significant decrease in the Atopic Dermatitis Severity index versus vehicle.⁵¹ The side effects experienced by the participants in these RCTs included mild application site pain and nasopharyngitis, but no serious or severe reactions were reported. Crisaborole's tolerability was also reported in an

open-label 48-week trial, in which the authors participated.⁵⁴ More than 500 participants received 4-week cycles of crisaborole as needed. Crisaborole was well tolerated in these patients, and no attributable serious adverse events were noted. Treatment-related adverse events included upper respiratory tract infection in approximately 10%; nasopharyngitis, cough, and pyrexia in 5–8%; atopic dermatitis flares in around 3%; and rare application site pain or infection. In contrast to TCS therapy, no atrophy, telangiectasia, or hypopigmentation was noted with crisaborole use.

Recently, crisaborole's efficacy and tolerability were established through two identically designed phase III clinical trials.⁵⁵ For these trials, the ointment was applied twice daily for 28 days in patients 2 years and older with mild to moderate atopic dermatitis. Two-grade or greater improvement in Investigator's Static Global Assessment score was the primary endpoint. Decrease in disease severity was quantified using erythema, excoriation, exudation, induration or papulation, and lichenification scores—a standardized measure of the severity of clinical signs in AD, such as the Eczema Area and Severity Index (EASI) or Scoring Atopic Dermatitis (SCORAD), was not used. A pruritus score, measured on a scale of 1 to 4, was also included. The study included 1522 randomized patients; 1016 received crisaborole and 506 received vehicle. Statistically significant improvements in Investigator's Static Global Assessment score, disease severity, and clinical signs of AD were noted as early as day 8 in the crisaborole ointment group compared with vehicle. Crisaborole was well tolerated, and application site pain was the most common adverse effect, present in 4.4% of crisaborole- and 1.2% of vehicle-treated patients. This reaction was short lived in most patients; 77.6% had resolution within 1 day of onset.

This novel therapy offers an alternative to TCS and TCI in the treatment of AD. Although TCS are associated with the development of telangiectasia and skin atrophy, and TCI have a high incidence of application site burning, crisaborole is associated with almost negligible short-term side effects.⁴⁴ Additionally, a recent vehicle-controlled study reported that crisaborole ointment application to sensitive areas was as well tolerated as vehicle.⁵⁶ This drug has received FDA approval to be marketed at Eucrisa. Interestingly, it is the first drug approved for use in AD without data from a standardized clinical features severity assessment score, such as EASI or SCORAD, in phase III RCTs. Further long-term investigational studies of crisaborole that include a standardized severity assessment score are needed, and studies for children younger than 2 years and further postmarketing studies are expected in the future.

MM36

A phase II clinical trial has recently been completed for another PDE-4 inhibitor, being developed by Medimetrics and Otsuka Pharmaceutical Development & Commercialization Inc., with the trial name MM36 (previously OPA-15406). The trial included 121 patients between the ages of 10 and 70 with mild to moderate AD.⁵⁷ The patients were randomly

assigned to either a 0.3% or 1% OPA-15406 ointment or vehicle twice daily for 8 weeks. Investigators reported a 31.4% improvement in mean EASI scores in the 1% OPA-15406 arm at 1 week, which continued to improve through week 8, with smaller treatment effects in the 0.3% OPA-15406 group. IGA scores rapidly improved in the 1% treatment group starting at 2 weeks compared with minimal change in the other two groups during this time. Overall, the rate of adverse events was similar for both treatment groups and vehicle. Adverse events in the OPA-15406 groups included worsening of AD in three patients with application site erythema, irritation, pain, and/or pruritus. No severe reactions occurred. OPA-15406's efficacy and tolerability in this population have been proven, and it warrants further investigation in phase III trials.

RVT 501

A randomized, investigator-blinded, vehicle-controlled phase II clinical trial has recently been completed for a novel Japanese PDE-4 inhibitor produced by Eisai Co., Ltd. with the trial name RVT 501 (previously E6005), now licensed to Roivant Sciences Inc. The trial included 81 participants and examined the effects of incremental E6005 concentrations from 0.01% to 0.2% over a 10-day period. Overall a dose effect was identified, and there was a clinically significant decrease in EASI score, SCORAD index, and the objective SCORAD index in the 0.1% and 0.2% groups compared with vehicle.⁵⁸

Janus kinase inhibitor tofacitinib

Janus kinase and signal transducer and activator of transcription form a signal transduction pathway. Many cytokines, such as IL-4, IL-13, and IL-31 (pruritus-specific interleukin), use this pathway. Tofacitinib (Pfizer), a small-molecule Janus kinase inhibitor, has been reported to directly inhibit these cytokines and reduce inflammation.⁵⁹ Topical tofacitinib has been investigated as a treatment for AD, and researchers⁶⁰ recently published data from a phase IIa clinical trial. Patients aged 18 to 60 years old with mild to moderate AD were treated twice daily for 4 weeks with either vehicle or 2% tofacitinib ointment. The tofacitinib group had significant improvement in pruritus by day 2, followed by an improvement in EASI and Physician's Global Assessment scores by week 1. Treatment-associated adverse effects included nasopharyngitis, contact dermatitis, headache, and increased blood creatine phosphokinase; however, application site reactions were more common with vehicle. Accordingly, topical tofacitinib has been found to be relatively well tolerated and superior to vehicle in the treatment of AD, but further studies to further are required to determine efficacy and long-term safety profile.

CRTH2 antagonism—Q301

CRTH2 is a transmembrane prostaglandin D2 receptor expressed on T_H2 lymphocytes. Stimulation of these receptors

leads to chemotaxis and activation of T_H2 cells.⁶¹ A new topical cream, Q301 (Qurient Co. Ltd.), is thought to antagonize the CRTH2 receptor and decrease the T_H2 response in AD. A phase II RCT comparing twice-daily administration of Q301 with vehicle in patients with moderate to severe AD over 8 weeks was recently completed (NCT02426359). The study results have not been published.

Antipruritic agents

Itch drastically contributes to patients' decreased quality of life and has been recognized as an essential feature to be included in objective atopic dermatitis severity scales.⁶² Accordingly, many new agents are being created to specifically target pruritus without altering the clinical signs of AD. CT327 is one such pruritus-specific agent, which has been found to inhibit capsaicin responses in sensory neurons and improve itch in psoriasis. A phase II clinical trial (NCT01808157) has been completed, but results have yet to be published.

Other agents

Multiple studies of potentially useful topical agents are listed on www.clinicaltrials.gov, including those with defined mechanisms of actions (eg, leukotriene inhibitors) and others designated only by study numbers. Aside from antipruritic agents and the CRTH2 antagonist Q301, only published studies that have completed phase II and beyond have been included in this review.

Alternative and adjunct therapies

Numerous other agents have been suggested for treating AD. Although some have evidence to support their use, others may have little effect on AD and may even be harmful (see the contribution on "Selected active naturals for atopic dermatitis"⁶³ in this issue).

Moisturizers

Moisturizers may be used as a primary treatment in mild disease and as an adjuvant in more severe manifestations. Emollients, humectants, and occlusive agents help treat the dysfunctional epidermal barrier in AD by lessening the resulting TEWL and xerosis.³⁴ Our study determined that moisturizers should be applied after bathing and drying to reduce additional TEWL that may result from wet skin.⁶⁴

Wet-wrap therapy

Wet-wrap therapy involves the use of a topical treatment covered by an occlusive bandage and is an effective adjuvant treatment in severe or refractory AD.^{65,66} A wet first layer is followed by a dry layer of bandage. Although uncomfortable, wet-wrap therapy increases the time allowed for topical

therapy penetration and provides a physical barrier to prevent scratching and TEWL. Researchers⁶⁷ found that 5%, 10%, and 25% dilutions of fluticasone propionate under wet-wrap therapy were equally effective; however, the 5% and 10% dilutions were associated with less hypothalamic-pituitary-adrenal axis suppression. Whether or not wet-wrap therapy is associated with increased risk of cutaneous infections is unclear.^{68,69}

Coal tar

A group has found *in vitro* coal tar to increase levels of filaggrin expression and inhibition of the IL-4 signaling pathway.⁷⁰ Coal tar preparations have some clinical use, and one study found their efficacy to be similar to 1% hydrocortisone acetate cream.⁷¹

Prescription emollient devices

Prescription emollient devices (PED) are a class of moisturizers specifically designed to target the epithelial defects in AD. PEDs contain specific proportions of lipids, including glycerylric acids, palmitoylethanolamide, or other hydro-lipids, and attempt to replicate the *in vivo* compositions of these substances.³⁴ Although PEDs have been approved as 510(k) medical devices, they are expensive and have not been proven to be superior to other moisturizing products in head-to-head trials.⁷²

Topical antimicrobials

Staphylococcus aureus is a common colonizer of skin in AD. These bacteria may be involved in the pathogenesis of AD by triggering multiple inflammatory cascades through their toxins, which damage the epidermal barrier and allow allergen penetration.³⁴ Antimicrobial and antiseptic preparations allegedly treat AD by decreasing the burden of these bacteria on the skin; however, a 2010 Cochrane review of RCTs did not find sufficient evidence to support this claim.⁷³ Accordingly, these treatment should be avoided in cases of AD without clear evidence of infection because they have not been found to have benefit and may contribute to microbial antibiotic resistance.

Topical antihistamines

Treatment with topical antihistamines, such as doxepin, is not recommended because they may cause local reactions, such as burning or stinging. They also carry the risk for systemic absorption, causing tiredness.^{74,75}

Gaps in knowledge

PDE-4 inhibitors will soon make their way into clinical practice. Their tolerability and efficacy have been shown in

clinical trials up to 48 weeks in length; however, more long-term studies and postmarketing surveillance are appropriate to assess adverse events that may only be apparent at the population level. Current treatments, such as TCS and TCI, require further investigations as well. Although there are data supporting the tolerability of long-term, intermittent use of TCS and TCI, head-to-head comparative studies with agents of relatively equal strength are needed to define the best agent.¹⁷

A desire for safe, effective, and economic therapeutics without the need for new drug development may lead to the optimization of currently available treatment modalities. The use of multiple alternating or concurrent treatment modalities such as TCS, TCI, and PDE-4 inhibitors as a part of a single regimen may lessen costs while decreasing disease severity. Studies are currently investigating the use of multiple concurrent treatments on a single patient with AD. Although this may be an area of research that revolutionizes this field, further exploration is needed.

Finally, the pathogenesis of AD has been hypothesized, but there are still many areas, such as patient genetics, environmental factors, and cellular mechanisms, that require further investigation. Broadening our understanding of AD and its pathogenesis will likely open new avenues for the treatment, management, and primary prevention of this disease.

Conclusions

AD is a heterogeneous disease with a complex pathophysiology. The disease may differ based on the patient's environmental exposures, ethnic group, geography, genetics, and unique pathophysiologic pathways.² Belief in a single agent to cure patients from AD is likely a fallacy. Biologic therapies and targeted small molecules are another evolutionary step in AD therapy and, together with new topical agents, have revitalized this previously stagnant field. Crisaborole has received FDA approval, and this PDE-4 inhibitor will be the first alternative topical therapy to TCS since the introduction of TCIs at the turn of the 21st century. As physicians and scientists increase their understanding of the pathophysiology of AD, we will gain insight into the best use of biologic therapies for the individual and, in turn, have an impact on society as a whole.

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