

Assessing the New and Emerging Treatments for Atopic Dermatitis

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■ Abstract

The newer and emerging treatments for atopic dermatitis (AD) focus on blockade of inflammatory cytokines, especially those that derive from T helper cell type 2 (T_H2) and are associated with a pathway of immunoglobulin E (IgE) sensitization. Among the proinflammatory cytokines that have been identified as promising therapeutic targets are chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTL_H2), IgE, thymic stromal lymphopoietin (TSLP), and several monoclonal antibodies that block key cytokine pathways in the innate immune response. Two agents that have been studied in phase III clinical trials are the boron-based phosphodiesterase-4 (PDE-4) inhibitor, crisaborole, and dupilumab, an antibody that inhibits the interleukin-4/IL-13 receptor α chain.

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■ Keywords

Atopic dermatitis; crisaborole; dupilumab; interleukin inhibitors; petrolatum; skin barrier

A large body of work has been published within the past decade providing newer insights on the pathophysiology of and immunologic factors involved in atopic dermatitis (AD). Research has demonstrated that AD is a

disease of both skin barrier dysfunction and T helper cell type 2 (T_H2)–driven inflammation, and that it is commonly associated with other atopic diseases, including food and respiratory allergies (Figure). These insights have been used as the foundation for more recent work to explore improved strategies for prevention, early intervention, and amelioration of AD.

Early Therapy and AD Prevention

Research has shown that the skin barrier is an important site for both the initiation of AD and allergic sensitization to protein antigens.¹ A wide range of potential preventive measures have been explored, with varying results. One AD prevention strategy that is supported by convincing evidence is enhancement of the skin barrier beginning in infancy.

Consistent with pathogenesis studies showing that increased transepidermal water loss (TEWL) in infancy is associated with an increased risk for AD, a preliminary study—called the Barrier Enhancement for Eczema Prevention (BEEP) study—was conducted to determine the feasibility of performing an early intervention study of emollient use in high-risk patients that would begin in infancy.² The primary endpoint of the feasibility study was to determine whether families would be willing to have their children randomized to a group that received no emollient application (unless the child's skin was clinically dry) or to an intervention group. Infants in the intervention group were to receive daily applications of topical emollients, starting at 3 weeks of age and continuing throughout the duration of the study.

In addition to determining that 42% of families agreed to be randomized, the team also collected data on the development of AD in both the intervention and control groups. Although this was a small sample size and the study was not designed to determine AD prevention or safety of daily emollient use, the investigators reported a large reduction in risk for AD development in the emollient group. In addition, they found that emollients were well tolerated, and no differences in adverse events were noted between the emollient and no emollient groups.

Other authors also have reported beneficial results from use of emollients beginning in infancy.^{3,4} These findings have prompted the launch of larger trials in both the United States and the United Kingdom. If these studies confirm the efficacy and safety of emollient therapy, this simple and low-cost intervention has the potential to reduce the global burden of allergic diseases.

New and Emerging Therapies for AD

The rationale for the development of new and emerging treatments for AD is the blockade of known inflammatory mediators. To date, the cytokines that have been identified as important in AD are those that derive from T_H2 cells, namely interleukin (IL)-4, IL-5, and IL-13, which are associated with increased production of immunoglobulin E (IgE) and, subsequently, IgE sensitization. However, the clinical efficacy of

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blocking a specific cytokine or other inflammatory mediator must be tested for each molecule. For example, although tumor necrosis factor (TNF) is expressed in skin and bone cells, TNF blockade has not been shown to be effective in established AD.⁵ However, several proinflammatory molecules involved in AD that have been identified as promising therapeutic targets include phosphodiesterase-4 (PDE-4), chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRT_H2), IgE, thymic stromal lymphopoietin (TSLP), and several monoclonal antibodies that block key cytokine pathways in the innate immune (T_H2) response, including IL-4/IL-13 receptor α chain, IL-13 alone, IL-22, and IL-31.

Although a number of novel agents for the treatment of AD currently are in development, this article addresses in depth only those for which phase III studies have been completed or are nearing completion, and briefly discusses several agents that are being tested in phase II clinical studies (Table).

PDE-4 Inhibitors

Since 1996, research has shown that PDE activity is increased and intracellular cyclic adenosine monophosphate (cAMP) levels are decreased in the peripheral blood leukocytes of patients with AD.⁶ The goal of inhibiting PDE is to increase intracellular cAMP levels and reduce cytokine mediator release. Both topical and systemic PDE-4 inhibitors have been investigated for the treatment of AD.

A topical PDE-4 inhibitor, crisaborole, integrates a boron ring into the cyclic structure of this agent. This low-molecular-weight compound effectively penetrates skin and accesses target cells. The addition of boron is thought to increase stability and have an impact on the target-binding capacity and selectivity of crisaborole.

Boron is a chemical element present in high concentrations in common foodstuffs (including chickpeas, almonds, beans, and apples); the skin absorption levels of boron are similar for crisaborole and dietary intake of boron-containing foods.

In an open-label phase IIa study, Tom and colleagues⁷ studied the safety, tolerability, and pharmacokinetic profile of crisaborole topical ointment 2% in 23 adolescents, 12 to 17 years of age, with AD lesions involving between 10% and 35% body surface area (BSA). The patients applied the ointment twice daily to affected areas, for a total of 28 days.

One patient discontinued the study because of application site dermatitis. Application site pain (in three patients) and nasopharyngitis (in three patients) were the most commonly reported adverse events; 19 adverse events were reported in 10 patients. The efficacy measures were mean Investigator's Static Global Assessment (ISGA) score and AD sign and symptom severity score. Assessment at day 29 showed that eight patients (35%) had achieved an ISGA score of 1 or lower, with at least a 2-grade improvement; the mean treatable BSA in the study population was reduced to 8.2% from a baseline of 17.6%. Blood samples for pharmacokinetic study were collected on days 1, 2, 4, 6, 8, and 9; no significant drug-related laboratory abnormalities were seen, and minimal serum levels of crisaborole were reported.

In another phase IIa study,⁸ two comparable target lesions were treated in adults with mild to moderate AD. The patients were randomized in a double-blind assignment to apply either crisaborole ointment 2% or vehicle twice daily for 28 days to one of the two target lesions. The primary efficacy endpoint was a change from baseline in the Atopic

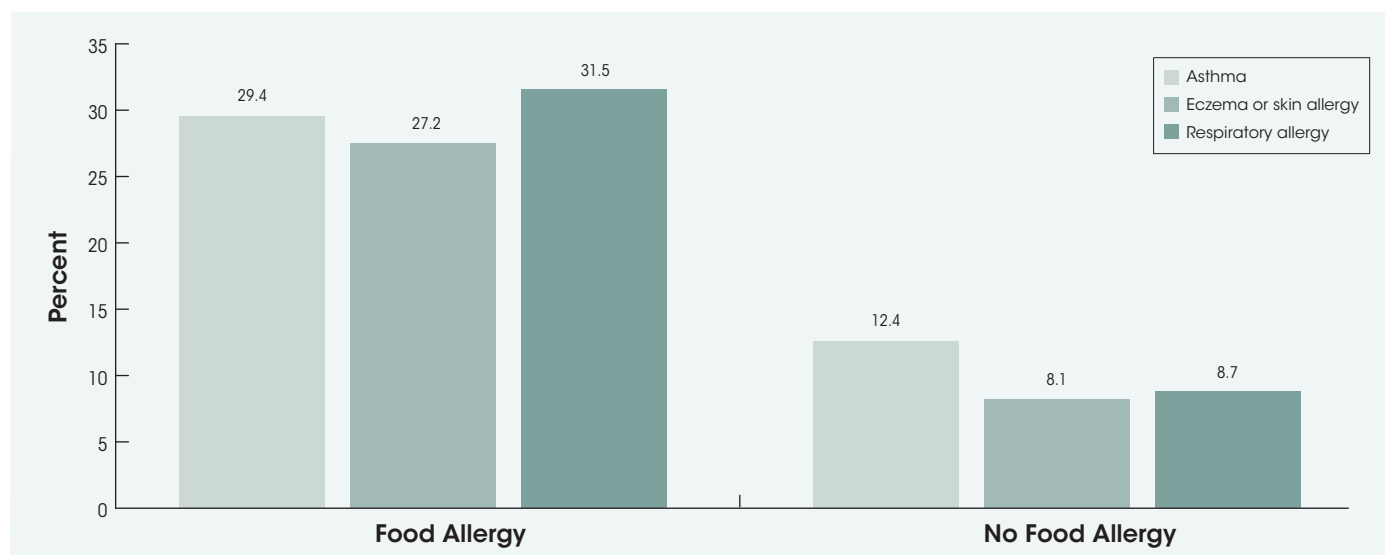


FIGURE Comorbid Food Allergy and Asthma, Eczema or Skin Allergy, or Respiratory Allergy in Previous 12 Months Among Children <18 Years of Age (%)

According to data reported by the National Center for Health Statistics, a National Health Interview Survey of about 9,500 children <18 years of age showed that an estimated 3 million (3.9%) reported having a food allergy within the past 12 months. These data, collected over a 10-year period (1997-2007), showed that children with food allergy are two to four times more likely to have related comorbidities such as asthma and other allergies. Approximately 27% of children with food allergy reported having atopic dermatitis or skin allergy; 8% of children without food allergy had such comorbidities. More than 30% of those with food allergy also had a respiratory allergy; 9% of children without food allergy had a respiratory allergy. The data also showed that children <5 years of age had higher rates of reported food allergy compared with those between 5 and 17 years of age, with boys and girls having similar rates of food allergy.

Source: Branum AM, Lukacs SL. Food allergy among U.S. children: Trends in prevalence and hospitalizations. NCHS data brief, no 10. Hyattsville, MD: National Center for Health Statistics. 2008.

■ **TABLE** New and Emerging Treatments for Atopic Dermatitis: Agents in Phase II or Phase III Clinical Trials

Compound	Mechanism of Action	Route of Administration
Currently in or completed phase III trials		
Crisaborole	PDE-4 inhibition	Topical
Dupilumab	IL-4/IL-13 receptor α -chain antagonism	SC injection
Currently in or completed phase II trials		
Apremilast	PDE-4 inhibition	Oral
Fevipiprant (QAW039)	CRT ₂ antagonism	Oral
ILV-094	IL-22 antagonism	IV infusion
Lebrikizumab	IL-13 antagonism	SC injection
Ligelizumab (QGE031)	IgE antagonism	SC injection
Nemolizumab (CIM331)	IL-31 receptor antagonism	SC injection
OPA-15046	PDE-4 inhibition	Topical
Q301	CRT ₂ antagonism	Topical
Tezepelumab (AMG157)	TSLP antagonism	IV infusion
Tralokinumab	IL-13 antagonism	SC injection
Ustekinumab	IL-23 p40 antagonism	SC injection

CRT₂=chemoattractant receptor-homologous molecule expressed on T_H2 cells; IgE=immunoglobulin E; IL=interleukin; PDE=phosphodiesterase; SC=subcutaneous; T_H2=T helper cell type 2; TSLP=thymic stromal lymphopoietin.

Sources: ClinicalTrials.gov. Laufer F, Ring J. Target-oriented therapy: Emerging drugs for atopic dermatitis. *Expert Opin Emerg Drugs*. 2016;21:81-89.

Eczema Therapies in Development; National Eczema Association. <https://nationaleczema.org/research/phases-drug-development>. Accessed May 19, 2016.

Dermatitis Severity Index (ADSI) score at day 28. At day 28, 17 of the 25 patients who received the study medication (68%) had a greater decrease in the ADSI score in the crisaborole-treated lesion than in the lesion treated with vehicle only; 5 patients (20%) had a greater decrease in the ADSI score in the vehicle-treated lesion than in the crisaborole-treated lesion. Three patients (12%) reported local application site reactions. No serious or severe adverse events were reported, and no patient discontinued the study because of an adverse event.

Two phase III, pivotal trials of crisaborole ointment 2% have been completed, involving a combined total of more than 1,000 patients treated with the study medication and more than 500 patients in vehicle groups. The average age of the patients in these studies was 12 years (range, 2 to 80 years of age). About one-third of the enrolled patients had mild AD and two-thirds had moderate AD; the mean BSA was about 20%.

The primary endpoint for treatment success (clear or almost clear skin plus two grades of improvement, with a statistically significant difference between the active-treatment and vehicle groups) was met in both phase III trials. An early separation of crisaborole versus vehicle response was seen as early as day 8, with a continued separation of response observed during the course of the study. The improvements in the different

objective signs of eczema were statistically significantly superior to the vehicle.

Treatment-emergent events, reported in about 11% of patients, included AD, application site pain, and, in a small percentage of patients, application site infection.

To date, long-term safety data that have been collected for 1 year—filed after completion of the phase III studies—appear to show that crisaborole has good tolerability and a low level of adverse events. Application site pain was observed, consistent with what was seen in the phase III studies. No significant adverse events were reported that were considered to be treatment-related. Importantly, no evidence of atrophy, telangiectasia, or hypopigmentation has been seen to date with the use of topical crisaborole ointment 2%. Other topical PDE-4 agents currently are in earlier stages of development.

The oral PDE-4 inhibitor, apremilast, currently approved by the US Food and Drug Administration (FDA) for the treatment of psoriasis, was studied in two open-label phase II trials to examine whether PDE-4 blockade could mediate the inflammatory cycle in AD. In one proof-of-concept study of 10 patients with either AD or contact dermatitis, the investigators found the medication to be safe, but efficacy results were described by the authors as “minimally effective.”⁹ In a second

study, Samrao and colleagues¹⁰ found promising results on clinical measures of efficacy; on gene ontology analyses, the investigators documented beneficial treatment-related alterations in immune response compared to baseline. A phase II multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of apremilast in patients with moderate to severe AD was completed in February 2016; results have not yet been published.

Anti-Interleukin-4 Receptor α -Chain Antagonist

Dupilumab, a subcutaneously administered anti-IL-4R α antibody, inhibits both IL-4 and IL-13 signaling by inhibiting the IL-4 receptor α subunit. This agent has shown promising results in a broad set of phase I and II studies in adults with AD.

Thaçi and colleagues¹¹ conducted a randomized, placebo-controlled, dose-finding, 16-week, phase IIb trial testing changes in both dose and frequency of administration. A total of 380 patients with moderate to severe AD whose symptoms were not adequately controlled with topical medications were randomized into six groups to receive 300 mg dupilumab every week (n=64), every 2 weeks (n=63), or every 4 weeks (n=65); or 200 mg every 2 weeks (n=61); 100 mg every 4 weeks (n=65), or placebo (n=61); 379 patients received at least one dose of the study drug.

The Eczema Area and Severity Index (EASI) at week 16 showed a 73% improvement in the high-dose group (ie, 300 mg per week) versus 18% improvement in the placebo group, a significant improvement ($P<0.0001$). However, lower doses also resulted in statistically significant improvements ($P<0.0001$ for all active-treatment groups) over placebo, although with proportionately lower percentages of EASI improvements. At the lowest dosage—100 mg every 4 weeks—EASI improvement was 44%.

Similar rates of treatment-emergent adverse events were seen in the dupilumab and placebo groups: 81% versus 80%, respectively; serious treatment-emergent adverse event rates were 4% in the dupilumab group versus 7% in the placebo group. The number of infectious adverse events was low in both the active-treatment and placebo groups. However, herpes simplex virus infections were seen in 26 of 318 patients (8%) in the dupilumab group and in 1 of 61 patients (2%) in the placebo group.

Two phase III, 16-week trials of dupilumab in patients with mild to moderate AD have been completed, and topline results have been announced by the manufacturer. The studies, LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2, identical in design, involved a total of 1,379 patients whose AD was not adequately controlled with topical agents or who were not candidates for topical medication.

The enrollment criteria included a score of 3 or 4 on the 5-point Investigator's Global Assessment (IGA) scale (0=clear to 4=severe); patients also were assessed at baseline using EASI and other measures of AD. Patients were randomized to receive dupilumab, 300 mg once weekly; dupilumab, 300 mg every 2 weeks; an initial loading dose of 600 mg of dupilumab, followed by placebo for 16 weeks; or placebo.

In the 300 mg/week dupilumab groups in SOLO 1 and SOLO 2, 37% and 36% of patients, respectively, achieved IGA scores of 0 or 1 (clear or almost clear); in the groups who received 300 mg every 2 weeks, IGA 0 or 1 was achieved in 38% and 36%, respectively. In the placebo groups in SOLO

1 and 2, IGA 0 or 1 was seen in 10% and 8.5% of patients, respectively ($P<0.0001$ for these treatment- vs placebo-group comparisons).

Improvements over baseline in EASI were 72% and 69%, respectively, in patients who received dupilumab, 300 mg per week, in SOLO 1 and 2. EASI improvements were 72% and 67%, respectively, in patients who received dupilumab, 300 mg every 2 weeks in SOLO 1 and 2. In the placebo groups, in both studies, EASI improvements were 38% and 31% ($P<0.0001$ for these treatment- vs placebo-group comparisons).

A 75% improvement in EASI (EASI-75) was seen in 52.5% and 48%, respectively, of patients who received the 300-mg weekly dosage of dupilumab in SOLO 1 and 2. EASI-75 was seen in 51% and 41%, respectively, of those who received dupilumab 300 mg every 2 weeks. In the placebo groups, 15% and 12% of patients, respectively, in SOLO 1 and 2 achieved EASI-75 ($P<0.0001$ for these treatment- vs placebo-group comparisons).

The overall rates of adverse events during the treatment period were 65% and 73% in the dupilumab groups in SOLO 1 and 2, and 65% and 72% in the placebo groups, respectively. Serious adverse events were seen in 1% and 3% of patients in the dupilumab groups, and 5% and 6% in the placebo groups. Injection site reactions and conjunctivitis were seen more often in the treatment groups; no patient discontinued the study because of an injection site reaction, and one patient dropped out because of conjunctivitis.

Interleukin-13 Inhibitors

Interleukin-13 has been shown to be highly expressed in AD skin on immunohistochemistry and transcriptome studies, and IL-13 gene polymorphisms are associated with increased AD risk. The rationale for the development of lebrikizumab and tralokinumab, IL-13 cytokine inhibitors, is that direct inhibition of IL-13 will have a therapeutic effect in AD. Both agents currently are undergoing phase II studies.

Thymic Stromal Lymphopoietin Antagonist

Tezepelumab, an inhibitor of thymic stromal lymphopoietin (TSLP), currently is being investigated in phase II studies. The cytokine TSLP is released by epithelial cells and keratinocytes (and, to a lesser extent, dendritic cells) during the process of allergen-related inflammation. TSLP has been shown to induce expression of IL-4, leading to a robust T_H2 response; the result of this process is upregulation of TSLP receptors and the consequent development of a positive feedback loop.¹²

Interleukin-31 Inhibitors

Several agents that inhibit IL-31 are currently being studied. One, nemolizumab (CM331), has progressed to phase II trials, with promising preliminary data¹³; others are in earlier stages of study. IL-31, which is secreted by activated T cells, has been identified as the key cytokine involved in causing pruritus.¹⁴ Some evidence also suggests that IL-31 may contribute to the development of AD.

Interleukin-22 Inhibitor

The IL-22 inhibitor, fezakinumab, is being studied in phase II trials in adults with AD. IL-22 has been found to be produced by CD4⁺ and CD8⁺ T-cell populations, referred to as T22; these cytokines are significantly increased in the skin of patients with AD.

Interleukin-12/23p40 Inhibitor

Ustekinumab, an IL-12/23p40 inhibitor approved for the treatment of psoriasis and psoriatic arthritis, is being studied as a treatment for AD in adults.¹⁵ The phase II study was completed recently, and publication of results is pending. A recent case report suggests the potential efficacy of ustekinumab in severe childhood AD.¹⁶

Janus Kinase Inhibitors

A phase IIa trial of topical tofacitinib was conducted in which the Janus kinase inhibitor was shown to substantially improve EASI in adult patients with mild to moderate AD.¹⁷ The use of oral tofacitinib for severe AD has been reported in an open-label study.¹⁸

Vitamin D

It is known that cathelicidins in the skin are relatively deficient in individuals with AD, and that vitamin D may mediate the expression of innate cathelicidins in the skin, although the literature is mixed on the possible mechanisms involved. Several intervention studies have been published on the possible effects on AD of oral vitamin D supplementation; these studies have yielded mixed results.¹⁹⁻²¹

Melatonin Supplementation

Chang and colleagues²² examined the possible role of melatonin in AD for its effects on sleep and disease severity in a double-blind, placebo-controlled, crossover trial of 48 children with more than 5% BSA involvement. The intervention was melatonin 3 mg/day for 4 weeks, with a 2-week washout and a crossover. The primary outcome measure was AD severity measured on the Scoring Atopic Dermatitis (SCORAD) index. Secondary outcomes included sleep variables such as sleep-onset latency and decreased mobility during sleep. The investigators reported a statistically significant difference in the SCORAD index (95% CI, -13.7 to -4.6; $P < 0.001$) with the use of melatonin. Improvements also were seen in sleep patterns, with decreases in both sleep-onset latency and mobility during sleep.

It is important to note that sleep improvement with melatonin can be seen in any population; this effect cannot be considered specific to AD. In addition, the statistically significant difference seen in the SCORAD index requires some closer consideration: the baseline SCORAD index was 49, indicating the highest level of moderate AD, on the border of severe AD; post-intervention, the SCORAD was 40, which is still at the highest level of moderate AD and on the border of severe AD. Thus, the study population had AD that was not optimally managed with this intervention. Nevertheless, it will be interesting to see future work using melatonin as adjuvant therapy in this population compared to traditional antihistamines.

Conclusion

Through research in animal models, several likely pathways for targeted treatment have been identified, and several new and emerging medications hold promise for the treatment of AD. In addition, early intervention to protect the skin barrier may be an effective method of preventing AD onset in genetically susceptible patients.

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