Emerging Therapies for Atopic Dermatitis

ABSTRACT

Atopic dermatitis (AD), also called eczema, is a chronic, relapsing inflammatory skin disease that is associated with significant morbidity and costs to patients and their families. Traditional AD treatments – including topical corticosteroids and topical calcineurin inhibitors – continue to be important in the management of AD, however, advances in our understanding of the pathogenesis of the disease have led to the development of new and emerging therapies.
**Introduction**

Atopic dermatitis (AD), or eczema, is a complex disorder involving skin barrier function abnormalities and skin inflammation. It is the most common skin condition in children under the age of 11 years, and its onset decreases substantially with age. In developed countries, AD is estimated to affect 15-20 percent of children, and prevalence appears to be increasing. While the reasons for the increasing prevalence have not been definitively established, large-scale studies suggest that disease expression may depend largely on environmental factors.

With its chronic, cyclical, and pruritic course, AD exacts a significant financial and emotional toll on those afflicted. Approximately 80 percent of children with AD develop asthma or allergic rhinitis later in childhood.

In this white paper, we will explore the pathophysiology of atopic dermatitis, as well as the rationale and mechanisms of action of existing and emerging therapies for AD.

**Pathophysiology of atopic dermatitis**

Recent research into the pathophysiology of AD indicates that the condition has a complex etiology involving multiple immunologic and inflammatory pathways and environmental triggers. Family history and genetics play a role, as well, with approximately 25 genetic susceptibility loci identified to date. The strongest known genetic link to AD is the filagrin (FLG) gene and FLG loss-of-function mutations are found in many, but not all, patients. FLG mutations lead to multiple biophysical defects in skin barrier function, including elevated pH, a disorganized...
stratum corneum, reduced lipid content, and increased transepidermal water loss (TEWL). Interestingly, elevated TEWL in newborns has been found to be a strong predictor of AD, independent of FLG gene status.\

The complex interactions between FLG gene defects and the environment are of great interest for better understanding the pathologic pathways involved in AD, including the initiation, maintenance, and promotion of the disease, which may help in identifying new targets for treatment.\

The unifying theory linking the various abnormalities associated with atopic dermatitis suggests that hematopoietic cells carrying abnormal genetic expressions of atopy cause clinical disease once they infiltrate the skin and mucosa. The proposed underlying mechanism may be either abnormalities in cyclic nucleotide regulation of marrow-derived cells or allergenic overstimulation.\

In practice, each patient’s disease phenotype is likely due to a unique interplay of several disease-specific dysregulated pathways. Of note, the distribution patterns of AD vary by age. In children, AD typically begins on the face. It then moves to the extensor surfaces of the extremities and becomes more accentuated in the antecubital and popliteal fossae over time. In adults, the pattern of distribution commonly includes the face, hands, and flexural areas of the neck, arms, and legs.\

Recent research has identified predictors of disease course and severity, including onset of signs and symptoms before 12 months of age and the presence of concomitant FLG gene mutations and immunoglobulin E (IgE) sensitization early in life.}

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**Figure 1. Age-related patterns of involvement in atopic dermatitis (AD)**

A. Children  
B. Adolescents  
C. Adults
Managing AD

Currently, there is no cure for AD and disease management is directed toward symptom relief, patient/parent education, and prevention of secondary complications. Traditional AD treatments – including topical corticosteroids and topical calcineurin inhibitors – are likely to continue to be important in the management of AD. However, newer and emerging therapies offer hope for patients with moderate to severe disease.

Existing treatments

Diligent moisturization and judicious use of topical corticosteroids remain the therapeutic standard for mild to moderate AD.

Topical calcineurin inhibitors (TCIs). Tacrolimus ointment and pimecrolimus cream are TCIs that act by inhibiting synthesis of proinflammatory cytokines. Tacrolimus is approved for:

+ Moderate to severe AD when there is no sufficient response or tolerance to conventional treatment

+ Supportive therapy of moderate to severe AD to prevent relapses and extend periods without recurrence in patients with frequent exacerbations who initially responded to treatment with tacrolimus ointment twice a day for a maximum of six weeks

Pimecrolimus is approved for mild to moderate AD when topical corticosteroids are contraindicated or not tolerated.

In practice, many dermatologists use TCIs for disease maintenance and reserve topical steroids for disease exacerbations.

In 2006, the FDA issued a requirement that both TCIs carry a boxed warning on their labels regarding a potential risk for malignancy. Two 10-year prospective patient registries were created to track malignancies in patients with AD treated with TCIs: A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety (APPLES) of tacrolimus and the Pediatric Eczema Elective Registry (PEER). Interim data from the APPLES registry is expected to be published some time in 2017.

Numerous epidemiological and clinical studies published over the past decade have failed to support an association between topical TCIs and malignancy, and the American Academy of Dermatology has not supported the FDA’s black box warnings.

Unfortunately, until very recently, treatment options for patients with severe AD have been quite limited. Systemic oral immunosuppressives such as cyclosporine are rarely justified and can have serious side effects.
Emerging therapies

Over the past decade, advances in our understanding of the pathogenesis of AD have paved the way for a number of new and potential treatments. These newer and emerging therapies focus on the inhibition of proinflammatory cytokines, including those that derive from T helper cell type 2 (Th2) - namely IL-4, IL-5, and IL-13, as well as phosphodiesterase (PDE)-4 and interleukin (IL)-4/IL-13 receptor \( \alpha \) chain.

Other proinflammatory mediators that have been identified as promising therapeutic targets include:

- Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2)
- Histamine H4 receptor
- IgE
- Thymic stromal lymphopoietin (TSLP)
- Monoclonal antibodies that block key cytokine pathways in the innate immune response, including IL-4/IL-13 receptor \( \alpha \) chain, IL-13 alone, IL-22, and IL-31

The hope is that, due to high specificity for their target molecules, biologics such as monoclonal antibodies will have fewer side effects than current immunosuppressive agents.

**Crisaborole.** This is a topical boron-based PDE-4 inhibitor. Research has shown that PDE activity is increased and intracellular cyclic adenosine monophosphate (cAMP) levels are decreased in the peripheral white blood cells of patients with AD. As such, the objective of inhibiting PDE is to increase intracellular cAMP levels and reduce the release of cytokine mediators. The addition of boron in crisaborole is thought to increase stability and to impact the target-binding capacity and selectivity of crisaborole.

Two pivotal Phase III trials of crisaborole ointment 2% have been completed, involving a combined total of more than 1,000 patients treated with study medication and more than 500 patients treated with vehicle. The primary endpoint for treatment in both studies was ‘clear’ or ‘almost clear’ skin plus two points of improvement on the Investigator’s Global Assessment (IGA) score, with a statistically significant difference between the active-treatment and vehicle groups. This endpoint was met in both Phase III trials, and separation of crisaborole versus vehicle response was seen as early as day eight of treatment. In the first Phase III study, 32.8 percent of patients treated with crisaborole achieved IGA success compared with 25.4 percent of vehicle-treated subjects. In the second Phase III study, 31.4 percent of crisaborole-treated patients achieved IGA success compared with 18.0 percent of vehicle-treated subjects.

Long-term safety data appear to show that crisaborole has good tolerability and a low level of adverse events.

Topical crisaborole was approved by the FDA for the treatment of AD in December 2016.

**Dupilumab.** This subcutaneously-administered monoclonal antibody inhibits the interleukin (IL)-4/IL-13 receptor \( \alpha \) chain, and has shown promising results in both Phase I and Phase II studies in adults with AD. In a 16-week randomized, placebo-controlled, dose-finding Phase IIb trial in adults with moderate to severe AD, patients treated with 300 milligrams of dupilumab per week showed a statistically significant 73 percent improvement in their Eczema Area and Severity Index (EASI) score at week 16, compared to 18 percent improvement in the placebo group.

Two 16-week Phase III trials of dupilumab have been completed in patients with moderate to severe AD whose disease was not adequately controlled with topical agents or who were not candidates for topical medication. In these studies, more than
one-third of patients treated with either 300 milligrams per week or 300 milligrams every two weeks achieved IGA scores of 0 or 1 (clear or almost clear) as compared to <10% of the vehicle treated patients. Patients treated with dupilumab also experienced significant improvements in EASI over baseline.

Dupilumab was approved by the FDA for the treatment of moderate to severe AD in March 2017.  

**Apremilast.** Currently approved for the treatment of moderate to severe plaque psoriasis, apremilast is an oral PDE-4 inhibitor that has been evaluated for the treatment of AD in a pilot study, with promising results. A Phase II multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study in patients with moderate to severe AD was completed in February 2016, but results have not yet been published. 

**Nemolizumab.** IL-13, which is secreted by activated T cells, has been identified as the key cytokine involved in causing AD pruritus. Nemolizumab is an IL-31 receptor antagonist that has been evaluated in Phase II trials with the goal of providing an improved treatment for AD-associated pruritus. In a global Phase II trial, the percent change in pruritus VAS (visual analog scale) at week 12, which was the primary endpoint, was significantly higher in the nemolizumab-treatment groups than in the placebo group (p<0.01). Phase III studies are planned to begin soon. 

**Lebrikizumab and tralokinumab.** These subcutaneously-administered IL-13 inhibitors are currently undergoing Phase II studies. IL-13 has been shown to be highly expressed in AD skin, so the rationale behind the development of IL-13 inhibitors is that direct inhibition of IL-13 will exert a therapeutic effect.

**Tezepelumab.** This inhibitor of TSLP is being investigated in Phase II studies. The rationale behind its development is that blocking TSLP will reduce allergen-related inflammation.
Fezakinumab. IL-22 is significantly increased in the skin of patients with AD. Fezakinumab is an IL-22 inhibitor currently being studied in Phase II trials in adults with AD.24

Ustekinumab. An IL-12/IL-23p40 antagonist, ustekinumab is approved for both moderate to severe psoriasis and psoriatic arthritis. It is currently being investigated in AD, as well.24

Conclusion
Over the past decade, research regarding the epidemiology, diagnosis, and course of AD has revealed new insights in our understanding of the disease, which has led to the development of novel therapies targeted toward blocking known inflammatory mediators. Due to the complex pathophysiology of AD, these new and emerging therapies will likely be incorporated in a multimodal approach to management where they are used in conjunction with standard treatments to optimize therapeutic outcomes while minimizing adverse impacts on both safety and cost.28
References


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Dr. Welgus has extensive experience in pharmaceutical R&D and in academia. He supported the development efforts of several companies through his own consultancy company and previously was Chief Medical Officer at Nycomed U.S. and Vice President and Head of Dermatology and Inflammation at Pfizer Global R&D in Ann Arbor, Michigan.

Dr. Welgus conducted research and taught dermatology at the Washington University School of Medicine in St. Louis for 18 years. He also led the Division of Dermatology at Jewish Hospital of Washington University and oversaw the Division of Dermatology at the VA Medical Center of St. Louis.

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