Therapeutic pipeline for atopic dermatitis: End of the drought?

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Activity Objectives:

1. To be able to name several targets of pharmacologic and biologic drugs in development for atopic dermatitis (AD) in the pathways of inflammation.
2. To know the mechanism of action of recently approved pharmacologic and biologic drugs for AD.
3. To describe the main differences in the cutaneous microbiome between AD skin and normal skin.

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Until the past year, our therapeutic armamentarium for treating atopic dermatitis (AD) was still primarily topical corticosteroids and, for more severe disease, systemic immunosuppressants. The pipeline of more targeted topical and systemic therapies is expanding based on our growing understanding of the mechanism for AD and is particularly focused on suppressing the skewed immune activation. Most agents are in phase 2 clinical trials. Crisaborole, a topical phosphodiesterase 4 (PDE4) inhibitor, became available in late 2016 in the United States for mild-to-moderate AD, with other PDE4 inhibitors, an agonist of the aryl hydrocarbon receptor, Janus kinase inhibitors, and commensal organisms also in trials for topical application. The first highly effective mAb for AD, dupilumab, targets the IL-4/IL-13 receptor and was approved in early 2017 in the United States for moderate-to-severe adult AD. Other biologics similarly inhibit T_H2 cytokines (thymic stromal lymphopoietin, IL-4, IL-5, IL-13, and the itch-specific cytokine IL-31 and their receptors) or T_H22/T_H17 cytokines, levels of which are increased in lesional skin. Orally administered small-molecule inhibitors that suppress inflammation (targeting chemoattractant receptor–homologous molecules expressed on T_H2 lymphocytes, PDE4, the histamine 4 receptor, and Janus kinase) or specifically itching (eg, NK1R inhibitors) are also being studied. Comparing biomarkers with individual responses to experimental agents will help to determine subphenotypes

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within AD that predict prognosis and treatment responses. (J Allergy Clin Immunol 2017;140:633-43.)

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Atopic dermatitis (AD; also known as atopic eczema) is one of the most common inflammatory skin disorders worldwide, with an increasing incidence during the past few decades, especially in developed countries. The point prevalence estimates in the United States are 11% to 13% for children[1,2] and 7% for adults.[3] AD is of at least moderate severity in 33% of affected children,[4] with the percentage increasing with advancing age.[2] Itch/pruritus is a hallmark of AD, and the associated discomfort of the disease and high visibility lead to sleep deprivation and adverse psychosocial effects.

A growing number of comorbidities are recognized to be associated with AD.[5] The propensity toward allergic disorders (food allergy, asthma, allergic rhinoconjunctivitis, and eosinophilic esophagitis) and skin infection (especially *Staphylococcus aureus* and widespread herpes/eczema herpeticum) is clearly increased, but neuropsychiatric issues (attention deficit hyperactivity disorder, depression, anxiety, conduct disorder, autism, and suicidal ideation)[6-10] have been linked more recently. Although earlier evidence suggested a link with cardiovascular disease,[11,12] more recent primary studies and meta-analyses have provided evidence against an association with AD.[13-16] Although the link with malignancy is also controversial, there is some evidence of an association of severe AD with lymphoma in cohort (but not case-control) studies,[17] possibly related to the chronicity of the inflammatory disease.

In addition, the economic burden is high, with the average annual cost conservatively estimated to be $5.3 billion in the United States[18]; out-of-pocket expenses can be as high as 10% of the household annual income.[19] Indirect costs are difficult to measure but include missed school or work and expenses associated with medical visits. These economic costs do not take into account the additional burden of comorbidities, which add another 150% in costs for associated allergic disorders alone.[20] The high prevalence, chronicity, costs for health care, and risk of comorbidities exert a profound negative effect on the quality of life of affected subjects, as well as their families.[18]

THE NEED FOR NEW THERAPEUTICS FOR AD

The mainstay of treatment for AD for decades has been topical corticosteroids. For more severely affected subjects, systemically administered broad immunosuppressant drugs (cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and short courses of systemic corticosteroids) are used.[21] Topical steroid use has been associated with largely cutaneous adverse events, most often skin thinning (atrophy and striae). Systemic agents all have several drug-specific risks and broadly suppress the immune system. Until this past year, the only new class of medications for treating AD contained the topical calcineurin inhibitors tacrolimus and pimecrolimus, which have been commercially available since 2000 and 2001, respectively. Although without the potential risks of topical steroids, topical calcineurin inhibitors have often been associated with burning/stinging and have had a black box warning associated with their use based on the early theoretic risk of increased nonmelanoma skin cancer and lymphoma.

Abbreviations used

AD:	Atopic dermatitis
AhR:	Aryl hydrocarbon receptor
CRTH2:	Chemoattractant receptor homologous molecules expressed on T_H2 lymphocytes
EASI:	Eczema Area and Severity Index
FLG:	Filaggrin
GRPR:	Gastrin-releasing peptide receptor
H4R:	Histamine receptor type 4
JAK:	Janus kinase
PDE4:	Phosphodiesterase 4
PoC:	Proof of concept
STAT:	Signal transducer and activator of transcription
TSLP:	Thymic stromal lymphopoietin

During the past decade, the underlying molecular basis for AD has been increasingly understood, particularly with a focus on barrier dysfunction, cutaneous and systemic immune abnormalities, and the role of the microbiome, allowing development of more targeted therapies.[22] Although debate has focused on whether AD pathogenesis is primarily "inside-out" (primary role of the immune system) versus "outside-in" (primary role of the epidermal barrier), it is now clear that the barrier, immune system, and microbes are all interconnected, with each abnormality progressively exacerbating another until successful intervention is introduced. In addition, the underlying basis for itch at the peripheral and central nervous system levels is an active area of investigation.[23] Importantly, our increased understanding of these factors that contribute to AD has enabled the development of new therapies targeted toward suppressing activated immune pathways, improving the epidermal barrier, normalizing the skewed microbial populations on affected skin, and reducing the itch. These emerging medications for AD can take the form of topical products (Table I), mAbs (Table II) or small-molecule inhibitors (Table III).

THE EFFECT OF CUTANEOUS IMMUNE RESPONSES ON THE SKIN BARRIER

The skin provides a barrier that protects from the external environment. This barrier is comprised of epidermal proteins of the stratum corneum, stratum granulosum, and tight junctions, as well as epidermal lipids, such as ceramides. When this barrier is impaired, external stimuli (eg, irritants, bacteria, and dust mite and food protein allergic triggers) can more easily induce inflammation.

During the past decade, several studies have demonstrated that skin barrier dysfunction is a critical component of AD.[24] Having high transepidermal water loss, a measure of barrier dysfunction, at 2 days of age is associated with a 7.1-fold higher increased risk of having AD by 1 year of age than having low transepidermal water loss.[25] In addition, having an inherited deficiency in epidermal barrier proteins (notably filaggrin [FLG]) increases the risk of AD and allergic disorders, presumably by attenuating the skin barrier, facilitating the interaction of external antigens with skin-resident immune cells and driving the cutaneous inflammation that leads to systemic immune responses.[24] These observations suggest that maintaining skin barrier function is important for the effective management of AD. However, even

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