The Future of Atopic Dermatitis Therapy

As new research elucidates the individual mechanisms of atopic dermatitis, the development of therapies that more directly influence the disease may change the scope of treatment.

BY JOOHO P. KIM, BA AND PETER A. LIO, MD

The journey to uncover the mechanisms underlying the chronic inflammatory skin condition atopic dermatitis (AD), which affects about 11 percent of the population, has been a challenging one. The complex interplay of immune dysregulation, allergen exposure, defective barrier functions of the skin, and Staphylococcus aureus colonization/infection has made it difficult to parse out a definitive pathway that causes this disease and the distinguishing etiopathological features of the various clinical subtypes of AD.

The current paradigm for the management of AD includes moisturizers, antibiotics, antipruritics, and anti-inflammatory therapies. While this combination therapy addresses the broader pathologic processes that define this group of eczematous diseases, gaps in our understanding of the pathogenesis of AD preclude more targeted treatment strategies.

Ahead, we will provide a preview of and the rationale behind several drugs in either phase 2 or 3 clinical trials that represent advances in our knowledge of the molecular basis of AD. The most dynamic area of drug development is the search for safer and more efficacious treatments targeting the inflammatory processes and immune dysregulation involved in AD. The past two decades have witnessed an explosion in the synthesis of the class of drugs known as biologics. Hundreds of these agents are currently being developed and investigated for pharmacologic therapy in numerous diseases.

Among these relatively newer medications, monoclonal antibodies and recombinant fusion proteins seem particularly promising for the treatment of eczema, as it is now possible to block with remarkable specificity various proteins that mediate inflammation and immune responses.

A brief detour looking at another inflammatory skin disease—psoriasis—might explain the excitement behind this class of drugs. Though distinct, psoriasis and AD share similarities in terms of a prominent inflammatory component driving both conditions. In fact, some of the same cytokines, for example tumor necrosis factor alpha (TNFalpha), interleukin 12 (IL-12), IL-17, and IL-22 to name a few, are implicated in both psoriasis and AD. Several biologics have been approved for the treatment of psoriasis. Among TNF-alpha inhibitors, etanercept...
(Enbrel, Amgen), infliximab (Remicade, Janssen), and adalimumab (Humira, AbbVie) have been proven effective in the treatment of moderate to severe plaque psoriasis.13-15 Ustekinumab (Stelara, Janssen), an anti-IL-12/IL-23 monoclonal antibody, is also quite beneficial for plaque psoriasis and psoriatic arthritis.16,17 In addition to these four biologics, the recent FDA approval in January 2015 of the fifth biologic secukinumab (Cosentyx, Novartis), an anti-IL-17 antibody) for the treatment of psoriasis further serves as an impetus to identify the biologics that are effective against AD.18,19

To date, however, the off-label application of biologics to AD has yielded limited data on the safety and efficacy of these drugs. Small prospective studies of various monoclonal antibodies against TNF-alpha (infliximab and etanercept), IgE (omalizumab), IL-5 (mepolizumab), and CD20 (rituximab) have demonstrated clinical improvement for a small percentage of patients, but larger studies need to be undertaken to better quantify the long-term clinical benefits and side-effect profiles of these drugs.8 Though there are no biologics approved for use in AD as of yet, there are several monoclonal antibodies in phase 2 and phase 3 clinical trials that could transform the treatment paradigm for eczema.

Antibodies against the following cytokines and cytokine receptors are currently being investigated: IL-31 receptor (CIM331), IL-22 (ILV-094), IL-13 (tralokinumab), IL-12/IL-23 (ustekinumab), and IL-4 receptor (dupilumab). All are in phase 2 clinical trials except for dupilumab, which is in phase 3.20 Two that we would like to highlight are ustekinumab and dupilumab (Table 1).

Ustekinumab, as discussed above, is FDA-approved for the treatment of plaque psoriasis and psoriatic arthritis.16,17 This anti-IL-12/IL-23 antibody is a particularly intriguing agent because one study showed that IL-12 p40 (the heavy chain subunit of the cytokine) expression is increased in atopic dermatitis skin lesions. Therefore, IL-12 might be a critical driver of inflammation in the disease, and therapeutically blocking its function could lead to significant clinical improvement.21 Thus far, reports have been somewhat mixed, with case reports of two patients who did not have an adequate response,22 and six who had significant improvement23-25 with ustekinumab. Proper randomized and controlled trials will hopefully elucidate whether or not there is a role for this drug in AD and if so, how it can be used optimally.

Dupilumab, which has led to remarkable improvement of disease severity in multiple studies, is in phase 3 trials to determine its safety and efficacy both as a monotherapy and as a combination therapy with topical corticosteroids.26 Not only does this medication block the action of one of the principal cytokines involved in the disease process, this antibody against the IL-4 receptor could partially allay the effects Staphylococcus aureus colonization has on exacerbating atopic dermatitis. One of the bacteria’s virulence factors—delta toxin—is known to stimulate the production of IgE and IL-4, aggravating the inflammation already present in the skin, which perhaps helps explain the beneficial effects of dilute beach baths.27,28 Thus, dupilumab, by blocking the receptor for IL-4, might avert some of the pro-inflammatory actions of the bacteria.

Biologics may be more effective medications for patients with refractory AD, as they specifically suppress

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**TABLE 1: EMERGING TREATMENTS FOR ATOPIC DERMATITIS**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of Action</th>
<th>Phase of Drug Development</th>
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<tbody>
<tr>
<td>Biologics</td>
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<tr>
<td>CIM331</td>
<td>Antibody against IL-31 receptor</td>
<td>2</td>
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<tr>
<td>ILV-094</td>
<td>Antibody against IL-22</td>
<td>2</td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>Antibody against IL-13</td>
<td>2</td>
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<tr>
<td>Ustekinumab</td>
<td>Antibody against IL-12 &amp; IL-23</td>
<td>2</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Antibody against IL-4 receptor</td>
<td>3</td>
</tr>
<tr>
<td>Anti-pruritics</td>
<td></td>
<td></td>
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<tr>
<td>CT327</td>
<td>Tropomyosin receptor kinase A kinase inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>VLY-686</td>
<td>Neurokinin 1 receptor antagonist</td>
<td>2</td>
</tr>
</tbody>
</table>

Adapted from the National Eczema Association’s “Eczema Drugs in Development” chart.20
the immunological pathways known to be implicated in the pathophysiology of the disease. Though more research is needed analyzing the long-term side effects of the drugs, they may also be safer alternatives to the non-specific immunosuppressive agents mentioned above in terms of serious adverse events. Of course, while these new medications have enormous potential in treating autoimmune diseases, inflammatory disorders, and cancers, biologics are incredibly expensive. Clinicians will have to evaluate the risks, benefits, and costs accordingly.

**ANTIPRURITIC AGENTS**

One of the principal symptoms of AD is pruritus. Despite this fact, at present there are no pharmacological treatments that specifically target the neural mechanisms that cause chronic itch, as multiple central and peripheral nervous system pathways mediate the pathology of pruritus. Besides their sedating effects, antihistamines seem to be of little or no benefit, and the only way to effectively control the patient’s pruritus is to manage the other aspects of the disease: i.e., with frequent moisturizer use, limiting the colonization and treating infections of the skin by *S. aureus*, and anti-inflammatory medications.

Possibly in the next five to 10 years, there will be new medications that change the way we manage pruritus in the setting of any dermatosis. CT327 and tradipitant (formerly VLY-868) are two medications in phase 2 of drug development that actually modulate the effect of nerve growth factor and substance P, respectively, on the sensation and perception of itch.

CT327 is a topical cream developed by a European company for the treatment of chronic pruritus in patients with AD or psoriasis. The medication suppresses the action of nerve growth factor (NGF) on trypomysin-receptor kinase A (TrkA) by blocking the receptor’s kinase domain, which is necessary for signal transduction. NGF appears to be implicated in the pathogenesis of pruritus by stimulating the growth of cutaneous sensory nerve fibers and sensitizing existing nerve fibers. The specific mechanism is thought to involve the up-regulation of transient receptor potential cation channel subfamily V member 1 (TrpV1) by NGF. CT327 seems to be the first TrkA kinase inhibitor tested for any clinical indication.

In a phase 2a study of 15 patients experiencing at least moderate pruritus with AD, the cream led to considerable improvement, especially of nocturnal pruritus, in just eight days. None of the patients experienced any serious side effects or skin reactions. CT327 was then tested in a cohort of 160 patients with psoriasis in a phase 2b study, which showed statistically significant differences between treatment and control groups in the improvement in pruritus Visual Analogue Scale (VAS) scores. Patients treated with CT327 had up to 59 percent improvement in itch symptoms after the trial. Again, the cream was found to be well-tolerated and safe with no systemic absorption. Data from this study was presented at the 72nd Annual Meeting of the AAD in March 2014.

Tradipitant, previously called VLY-686, is a medication being developed for chronic pruritus in AD. The drug is an antagonist of the neurokinin 1 receptor (NK-1R), which has a high affinity for the neurotransmitter substance P. Substance P is thought to be involved in pain perception, nausea, vomiting, stress, substance abuse, inflammation, and a variety of other pathophysiologic processes. As such, the potential clinical indications of NK-1R antagonists are very broad, such as alleviating the nausea and vomiting associated with chemotherapy and treatment for alcohol use disorder. The role of substance P in pruritus was demonstrated in a study in which the NK-1R antagonist BIIF 1149 CL significantly reduced scratching behavior in a mouse model of dermatitis. In addition, a similar molecule—aprepitant—has had some success with chronic pruritus in a variety of clinical settings, such as in patients with cutaneous T-cell lymphoma, further implicating substance P as a mediator of itch.

In a recent phase 2 proof of concept trial looking at the effect of oral tradipitant in patients with AD with a VAS score ≥ 70 mm, researchers found that higher blood concentrations of tradipitant was correlated with a greater improvement in VAS scores. Interestingly, they also found that the medication was more effective when administered in the morning, rather than in the evening. The mean change in VAS score for the treatment group was -54.0 mm, which was significantly better than the -30.3 mm change in the control group.
If these two medications are approved for clinical use, they would be some of the first drugs to target the symptom of pruritus itself in the setting of AD, rather than the traditional approach of managing the disease as a whole to control the itching. Clearly, there is a significant neural component to AD, and perhaps the promising phase 2 data on CT327 and tradipitant warrant more attention to this aspect of the AD treatment paradigm.

CONCLUSION: PATHWAYS CLEARING

This is an exciting time for physicians treating AD, as several therapies are under development that could considerably improve patients’ quality of life. The challenge with atopic dermatitis is that a myriad of pathways interact to produce the disease state. As we continue to dissect out the individual mechanisms, therapies that more directly influence the disease will surely be developed.

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