SPECIAL ARTICLE

New and developing therapies for atopic dermatitis*

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Abstract: Atopic dermatitis is a common inflammatory skin disease. New understanding in disease pathogenesis has led to a considerable number of promising new drugs in development. New topical agents can be especially helpful for children, providing an alternative to the need for chronic topical corticosteroid use. While many patients with mild or moderate disease can be managed with topical treatments, there are unmet needs for recalcitrant and severe cases. New and developing therapies hold promise for real advances in management of this complex disease.
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INTRODUCTION

Atopic dermatitis (AD) is a very common, chronic inflammatory skin disease affecting up to 20% of children and 10% of adults in industrialized countries.[1] Clinical features of AD include erythema, edema, lichenification, excoriations, oozing, and crusting. Pruritus is a crucial and dominant feature of AD and generates comorbidities such as sleep loss and psychological distress, creating a continuing disease burden for patients, parents and siblings.

AD pathogenesis is not clearly elucidated, though skin barrier defects and altered immune responses are accepted as key components in disease development.[2] Genetic and environmental factors strongly affect AD expression. Disease prevalence is increasing in developing countries, especially in urban regions.[1] Resultant from these many factors, AD displays significant heterogeneity in disease phenotype, age of onset, clinical severity, persistence, comorbidities and response to therapy. Despite our improved understanding of the molecular pathways in AD, most traditional therapies are not based on scientific mechanistic understanding.

The management strategy of AD relies heavily on current and past disease severity, along with comorbidities. The epidermal barrier plays an important role in eczema disease initiation. Initial management includes patient education, emollient therapy and trigger avoidance. Emollients have proven to reduce the incidence of AD[3,4] and can be equally effective as topical corticosteroid (TCS) of low potency.

The main therapeutic objectives are reductions in pruritus and skin inflammation and prevention of flares, while minimizing side effects. Management can be difficult and time consuming, requiring a multidimensional approach that includes patient/parent education, elimination of exacerbating factors, restoration of epidermal and skin barrier functions, combined with various pharmacologic therapies depending on disease severity.

MILD ATOPIC DERMATITIS

Usually successfully managed with a combination of TCS and general recommendations such as moisturizing, preventing heat and sweating and reducing psychological stresses.

MODERATE ATOPIC DERMATITIS

Usually requires topical therapy with TCS, possibly supplemented with topical calcineurin inhibitors. In patients with moderate

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to severe disease, topical therapies will often provide only temporary improvement, necessitating treatments that reduce inflammation such as phototherapy or systemic immunomodulating drugs.

SEVERE ATOPIC DERMATITIS

Current guidelines recommend the use of traditional immunosuppressant medications including cyclosporin (CYA), methotrexate (MTX), mycophenolate mofetil (MMF), and azathioprine (AZA) in patients who fail conventional topical therapy or phototherapy.[5,6]

While these traditional immunosuppressive therapies can show effectiveness in AD, their routine use is limited by often inadequate disease responses and by adverse effects. CYA, in optimal dosing levels of 5 mg/kg, gives the most rapid and beneficial effects whereas MTX and AZA provide only about 50% response rates in most studies.[5,7] Concerns about renal, hepatic and other toxicities tend to limit duration of treatment for these agents but they may be tapered and supplanted with ultraviolet light when the initial severe inflammation comes under control. Generally, treatment of moderate-to-severe atopic dermatitis is often frustrating in clinical practice for both patients and providers.

Biologic therapy holds promise for providing those patients who suffer from severe disease with effective, long-term options by virtue of their targeted effects on the dysregulated inflammatory responses that cause chronic and recalcitrant disease. As our specific understanding of the complex pathogenesis of AD improves, including immune and molecular pathways, a variety of experimental biologics are targeting these pathways with the hope of less toxicity and greater efficacy.

NEW TOPICAL THERAPIES

Phosphodiesterase (PDE) inhibitors (Crisaborole)

Patients with AD showed significantly elevated leucocyte PDE activity compared to non-atopic normal individuals or to patients with allergic contact dermatitis.[8] This PDE abnormality appeared to be a characteristic of atopic disease in general, since levels were also increased in patients with allergic rhinitis but no AD. Clinical consequences of the abnormal PDE activity included elevations in histamine release and IgE synthesis.

Following the demonstration of PDE abnormalities in AD, studies showed that the Type-4 PDE-inhibitor, RO-20-1724, could normalize basophil histamine release and lymphocyte IgE production in AD leukocytes.[9, 10]

These encouraging findings led to clinical trials of topical PDE inhibitors (PDEi) and provided evidence for efficacy greater than placebo but less than low potency TCS.[11] Such weak results, along with an array of mild systemic effects, led to a long hiatus in developing PDE agents for AD.

Several PDEi's have been in development, but only crisaborole ointment has been approved by the Food and Drug Administration (FDA) for topical use in AD patients as young as 2 years of age. The drug has efficacy in lessening inflammation and appears to relieve skin itching fairly early during therapy. It is well tolerated and the most common adverse effect was application site pain in 4.4% of the patients.[12] It is now an alternative therapy to TCS without the side effects such as telangiectasia and skin atrophy.

Janus Associated Kinase-Signal Transducer and Activator of Transcription (JAK – STAT) inhibitors (Tofacitinib)

JAK pathway is used by many cytokines involved in AD. The JAK inhibitor tofacitinib has been shown to inhibit cytokines such as interleukin (IL) 4 directly, leading to reduced inflammation.[13] Studies of its use in psoriasis, alopecia areata and AD are currently ongoing.

A phase IIa trial showed that twice daily topical tofacitinib 2% had significant efficacy when compared to vehicle ointment.[14] Topically-delivered JAK inhibitors are a promising therapy, but further studies in AD patients are needed.

NEW AND EMERGING SYSTEMIC THERAPIES

Anti IL-4 and IL-13 (Dupilumab)

Dupilumab is a fully-humanized, monoclonal antibody targeting the alpha subunit of the IL-4 receptor to block signaling of IL-4 and IL-13. Early phase I and II trials demonstrated its effectiveness in improving the symptoms of adult patients with AD in a dose dependent manner.[15,16]

An in-depth study of lesional and non-lesional skin during dupilumab therapy found that modulating IL-4/IL-13 signaling through IL-4Rα antagonism in patients with AD had statistically significant and dose-dependent improvement in the AD transcriptome after 4 weeks of treatment, compared with placebo.[17] The authors also demonstrated that dupilumab suppressed mRNA expression in lesional skin of genes related to activation of T cells, dendritic cells, eosinophils, inflammatory pathways, and type 2 cytokines. By use of microarrays and quantitative RT-PCR they demonstrated that genes responsible for epidermal hyperplasia (S100A and K16 genes) were also downregulated by dupilumab.[17] The authors speculated that blocking IL-4/IL-13 may not only improve inflammation in AD but may also restore skin barrier function as a result of significant increases in claudin, loricrin, filaggrin and lipid product levels. These results show promising new insights into the role of type 2 cytokines in AD and suggest that inhibition of IL-4/IL-13 has the potential to reverse multiple molecular defects in patients with AD.

In March 2017 the FDA approved the use of dupilumab for the treatment of adults with moderate-to-severe AD who are not adequately controlled with topical prescription therapies or for whom these treatments are not appropriate. The initial dose recommended is 600 mg (two 300 mg subcutaneous injections) followed by 300 mg given every other week. Although adverse effects were relatively few, conjunctivitis, injection-site reactions, nasopharyngitis, and upper respiratory tract infection are worth mentioning.[16] Topical ophthalmic anti-inflammatory medications were typically needed to control eye symptoms while other cases resolved spontaneously. Further studies regarding the etiology of the conjunctivitis and its resolution are needed.

Anti IL-13 (Lebrikizumab / Tralokinumab)

IL-13 appears to play a role in AD pathogenesis and it is overproduced in patients skin. It may reduce epidermal barrier integrity by decreasing gene expression of loricrin and involucrin.[18] A phase II clinical trial assessing the efficacy and safety of lebrikizumab in patients with AD concluded that blocking IL-13 with leb-

rikizumab in moderate-to-severe AD provides significant improvements in a number of severity outcomes.[19] Dosing every 4 weeks markedly improved the percentage of patients achieving the primary and secondary endpoints. It is important to note that these improvements were seen on the background of daily TCS application, probably explaining the high placebo response rates.

Tralokinumab is a human monoclonal antibody also targeting IL-13. Ongoing studies have shown some improvement at higher dose, but TCS therapy in the placebo groups, similar to the lebrikizumab trials, also likely blunted the statistical significance.[20]

In sum, blockade of IL-13 alone appears to have an effect but interpreting the results of trials of lebrikizumab and tralokinumab are obscured by the heavy background use of TCS. It is unknown whether the effect size of blocking IL-13 alone will be similar to IL-4/IL-13 dual blockade until further studies are performed.

PDE4 inhibitor* (*Apremilast)

Apremilast is an oral PDE4 inhibitor approved by the FDA for the treatment of obstructive pulmonary disease, plaque psoriasis, and psoriatic arthritis. Its safety and efficacy in AD adult patients were investigated in an open-label pilot study that showed significant reduction in pruritus and DLQI (Dermatology Life Quality Index) and analyses also revealed alterations in immune response pathways.[21] Since then, its successful use in chronic, severe, and recalcitrant AD and eczematous disorders has been reported, but larger randomized controlled studies are needed.[22]

Anti-IL-31 (Nemolizumab)

IL-31 is a Th-2 cell product believed to be a major pruritogenic inflammatory cytokine.[23] It also amplifies proinflammatory cytokine secretion, disrupts epidermal barrier function by affecting epidermal terminal differentiation and lipid constituents, and recently was found to activate signal transduction cascades, such as the JAK-STAT pathway.[24] Hence, it was hypothesized that blocking IL-31 or its receptor would be effective in the treatment of patients with AD.

Nemolizumab is a humanized monoclonal antibody against IL-31 receptor A. A phase II placebo-controlled trial assessing efficacy and safety in 264 patients with moderate to severe AD showed significant improvement and efficacy.[25] The primary endpoint was the improvement in pruritus compared with placebo. Secondary efficacy outcomes included improvement from baseline in the EASI (Eczema Area and Severity Index), SCORAD (Severity Scoring of Atopic Dermatitis), sIGA, (static Investigator's Global Assessment), body surface area, pruritus verbal rating scale, and sleep disturbance. In the two highest dosing groups, participants also experienced 59-63% reductions in sleep disturbance. Disease severity was also reduced, though not as robustly as the antipruritic effects. Nemolizumab subcutaneous injections were well-tolerated with adverse effects mostly in AD exacerbations. Targeting IL-31R appears to provide significant itch relief in patients with AD in a dose-dependent manner. Further studies are warranted to better clarify the effects on skin inflammatory lesions and to further understand the side effect profile.

CONCLUSIONS

Therapies for AD have long been relatively stagnant with few dramatic breakthroughs. While new topical therapies are emerging, none has yet matched the efficacy of mid-strength TCS. That approach has been hampered by "steroid phobias" and misleading claims of "steroid addiction", in part a consequence of over-prescribing by physicians, but also from emotion-based internet-generated fears.[26] Clearly there remains a need to find more potent topical agents with fewer side effects. The most gratifying advances in AD therapy have come from better understanding of immune and inflammatory mechanisms. The shining example is the development of dupilumab which has shown remarkable reduction in clinical severity with relatively few adverse effects. The many other new compounds in the pipeline should continue to provide real advances in management of this severe, common and complex disease. ❑

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