Atopic Dermatitis Pipeline

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Just when you might have thought dermatologic therapies were peaking, along came another banner year in atopic dermatitis (AD). Last year we saw the landmark launch of dupilumab, the first US Food and Drug Administration (FDA)–approved biologic therapy for AD. Dupilumab addresses a novel mechanism of AD in adults by blocking IL-4 and IL-13, which both play a central role in the type 2 helper T cell (T_H2) axis on the dual development of barrier-impaired skin and aberrant immune response including IgE to cutaneous aggravating agents with resultant inflammation. Additional information has shown direct effects to reduce itch in AD.[1] A 12-week study of dupilumab monotherapy showed that 85% (47/55) of treated patients had at least a 50% reduction in Eczema Area and Severity Index (EASI) score and 40% (22/55) were clear or almost clear on the investigator global assessment. With concomitant corticosteroid therapy, 100% of patients achieved EASI-50.[2] Also notable, 2017 ushered in the appearance of a novel iteration of the 30-year-old concept of phosphodiesterase inhibition with the approval of the topical agent crisaborole for AD treatment in patients 2 years and older, which has been shown to be effective in both children and adults.[3,4] However, despite these leaps of advancement in the care of AD, by no means has the condition been cured.

Atopic dermatitis has remained an incurable disease due to many factors: (1) variable immunologic and environmental triggers and patient disease course; (2) intolerance to therapeutic agents, including an enhanced sense of stinging and/or reactivity; (3) poor access to novel therapies among underserved patient populations; (4) lack of available data and information on variable treatment response by ethnicity and race; and (5) the absence of biologic treatments for severe childhood AD to modify long-term recurrence and progression of atopy, which is probably the most important issue, as the majority of AD cases start in children 5 years and younger.

Instituting a treatment today to provide children with disease-free skin for a lifetime truly is the Holy Grail in pediatric dermatology. To aid in the progress toward this goal, a deeper understanding of the manifestation of pediatric versus adult AD is now being investigated. It is clear that with adult chronicity, type 1 helper T cell (T_H1) axis activity and prolonged defects are triggered in barrier maturation; however, recent data have started to demonstrate that the youngest patients have different issues in lipid maturation and lack T_H1 activation. In particular, fatty acyl-CoA reductase 2 and fatty acid 2-hydroxylase is preferentially downregulated in children.[5] It appears that the young immune system may be ripe for immune modification, which previously has been demonstrated with wild-type viral infections of varicella in children.[6] However, future research will focus on what kind of tweaks to the immune system are required.

To encapsulate the AD pipeline, we will review drug trials that are in active recruitment as well as recently published data, which constitute an exciting group full of modifications of current therapies and agents with novel mechanisms of action. Paller et al[7] and Renert-Yuval and Guttman-Yassky[8] published detailed analyses of the recent pipeline for systemic therapies. In the realm of systemic agents, the main therapies in development are alternative immunomodulation mechanisms and biologic agents targeting a variety of immune checkpoints. Oral treatments and intravenous, intradermal, and subcutaneous injections will offer AD patients a variety of therapeutic options and potentially provide help for the needle-phobic patient.

Therapies targeting new mechanisms of action include Janus kinase (JAK) inhibitors, which have shown promising results for alopecia areata and vitiligo vulgaris. These agents may create selective modification of the immune system and are being tested topically and orally (Clinicaltrials.gov identifier NCT03011892). One phase 2a trial of topical tofacitinib showed superior efficacy over

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placebo, supporting class benefit, but drug development has been stopped for this agent.[9] Another recent phase 2 trial of systemic baricitinib plus topical corticosteroids for treatment of AD demonstrated good efficacy (ie, EASI-50) versus topical corticosteroids alone (61% vs 37%).[10]

Another mechanism that currently is being studied includes a topical IL-4 and IL-13 inhibitor, which would hopefully mimic the efficacy of dupilumab, antioxidant therapies, and antimicrobials (NCT03351777, NCT03381625, NCT02910011). A new G protein–coupled receptor 19 (also known as membrane-type bile acid receptor or TGR5 receptor) agonist represents a novel mechanistic approach (NCT03492398), as does the liver X receptors (LXR) agonist, which is intended to enhance barrier function and thereby reduce inflammation (NCT03175354). Ammonia-oxidizing bacteria are being tested with a putative mechanism of increased nitic oxide release (NCT03235024), while nitric oxide alone also is being tested (NCT03431610). Although most of the aforementioned agents are in phase 1 and 2 trials, excitement is mounting over a phase 3 trial for IDP-124 lotion (NCT03058783), though extensive data have not yet been released from the manufacturer, as well as a phase 4 trial for crisaborole in infants and toddlers aged 3 to 24 months (NCT03356977). If the trial is successful and the drug is approved, crisaborole would be the first FDA-approved topical nonsteroidal prescription agent for that age group. Interestingly, 2 systemic agents are being tested in children younger than 18 years with AD, including a phase 3 trial of PF-04965842, a JAK1 selective inhibitor, in children aged 12 years and older (NCT03575871), and a phase 4 trial of omalizumab in children aged 4 to 19 years (NCT02300701). Omalizumab is an anti-IgE antibody with indications for allergic asthma and chronic idiopathic urticaria.

Data on the outcome of a phase 3 trial of dupilumab in adolescents has been released but not yet published by the manufacturer and shows promising results in children aged 12 to 17 years, both in reduction of EASI score and in achieving clear or almost clear skin.[11] Interestingly, limited data available from a press release reported similar results with dupilumab injection every 2 weeks versus every 4 weeks, which may give alternative dosing regimens in this age group once approved[11]; however, publication has yet to occur for the latter data.

Other mechanistic agents include blockade of cytokines and interleukins, particularly those involved in type 2 helper T cell (T_H2) activity, such as thymic stromal lymphopoietin (a cytokine), as well as targeted single inhibition of IL-4, IL-5, IL-13, and IL-31 and/or their receptors. Nemolizumab, an anti–IL-31 receptor A antibody, is showing promise in the control of AD-associated itch and reduction in EASI scores.[12] Stem cell therapy, anti–OX-40 receptor monoclonal antibody, anti–IL-17C monoclonal antibody, anti–IL-33 monoclonal antibody, and neurokinin-1 receptor antagonist (NCT01941537, NCT03100344, NCT03054428, NCT03160885, NCT02888704, NCT03269773, NCT03568162, NCT03568071, NCT03533751, NCT03568331, NCT03540160) round out the roster of agents entering further trials in AD.

The future of AD therapy is anyone's guess. Having entered the biologic era with dupilumab, we have a high bar set for efficacy and safety of AD therapies, yet there remains a core group of AD patients who have not yet achieved clearance or refuse injectables; therefore, adjunctive or alternative therapeutics are still needed. Furthermore, we still have not identified who will best benefit long-term from systemic intervention and how to best effect long-term disease control with biologics or novel agents, and choosing the therapy based on patient disease characteristics or serotyping has not yet come of age. It is exciting to think about what next year will bring!

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