Novel therapies in the treatment of atopic dermatitis

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Atopic dermatitis (AD) is a common inflammatory cutaneous disorder, affecting up to 15% to 30% of children and 2% to 10% of adults.¹ The pathogenesis of AD is multifactorial, arising from an interplay of genetic and environmental factors that result in impaired barrier function, immune dysregulation, and disruption of the antimicrobial barrier. As our understanding of AD pathogenesis evolves, targeted therapies are being developed to inhibit underlying molecular pathways. The relative successes and failures of targeted therapies will inevitably influence our understanding of disease pathogenesis, allowing us to distinguish the relative importance of different cell types, cytokines, and growth factors in the many manifestations of AD and its associated comorbidities. In the current review, we will briefly discuss current perspectives on the pathogenesis of AD and summarize existing targeted therapies that address some of the key components of this disease.

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Abstract

Atopic dermatitis (AD) is a common cutaneous condition characterized by epidermal barrier disruption, severe skin inflammation, and pruritus. As a result of our growing understanding of disease pathogenesis, the therapeutic armamentarium to manage AD is rapidly expanding. Moving beyond broadly immunosuppressive agents, newer therapies for AD offer more targeted immunomodulation in the forms of phosphodiesterase 4 inhibitors, Janus kinase inhibitors, and anticytokine monoclonal antibodies. While such therapies are generally considered safer than traditional immunosuppressive agents that have been used off label for AD for decades, they are not without risk entirely. In some cases, potential side effects may be difficult to manage. This review summarizes current views on AD pathogenesis and discusses these novel and emerging therapies, including a discussion of the mechanisms of action, potential side effects, and limitations of current clinical trials for each drug. While the rapid and prolific expansion of therapies to treat AD is encouraging, additional studies are needed to adequately evaluate the long-term safety, efficacy, and generalizability among different age groups and disease subtypes.

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Disease pathogenesis: novel insights, new targets

Atopic dermatitis is characterized by a vicious cycle of barrier disruption, severe inflammation, and itch. Over the last two decades, over 46 genes that are associated with AD in humans and/or animal models of the disease have been identified.² It remains unclear what, if any, is the primary inciting factor for AD development. However, 2 major models, known as the “inside-out” and the “outside-in” hypotheses, have been proposed. The “inside-out” hypothesis postulates that AD is primarily driven by aberrant immune signaling, whereas the “outside-in” theory suggests that atopic disease results from a primary defect in epidermal barrier with subsequent immune activation. In reality, AD likely results from a complex interplay of the 2 models as well as other cellular and molecular factors that are still under investigation.

Immune abnormalities in AD include innate and adaptive immune dysfunction. The type 2 T helper cell (Th2) immune response plays an important role, especially cytokines interleukin (IL)-4, IL-13, and IL-31.³,⁴ IL-4 and IL-13 inhibit expression of epidermal barrier proteins and production of antimicrobial peptides (AMPs), predisposing AD patients to Staphylococcus aureus infection.⁵,⁶ IL-4, IL-13, and IL-31 may also contribute to itch, a central symptom of eczema lesions.⁷ Dorsal root ganglia (DRG) neurons from mice and humans express receptors for these cytokines and may be directly activated when treated with them in culture.⁸ Moreover, large increases in IL-31 are seen in acute AD lesions and may correlate with disease severity.⁹,¹⁰

In addition to immune dysfunction, epidermal barrier dysfunction is another significant driving force in AD pathogenesis. In both affected and unaffected skin of AD patients, structural proteins and lipids are reduced, leading to barrier dysfunction and lack of water retention.¹⁰ One such protein is filaggrin (FLG), whose breakdown products—pyrrolidone carboxylic acid and urocanic acid—promote skin hydration and protect against ultraviolet rays.¹¹ These acids lower skin pH and have been shown to reduce activation of serine proteases and affect bacterial growth.¹¹,¹² Mutations in FLG allow microbial pathogens to penetrate the skin, leading to allergic sensitization and infections.¹³ Other proteins that influence barrier function, including the serine protease inhibitor lympho-epithelial Kazal-type-related inhibitor, loricrin, and involucrin, may be mutated in AD or AD-associated diseases.¹⁴,¹⁵

With impaired immune function and epidermal barrier disruption, patients with AD may have altered cutaneous microbial colonization. Atopic patients exhibit lower levels of AMPs, proteins that stimulate the immune system to fight off microbial pathogens, which results in an imbalance of microbes and commensal bacteria.¹⁶,¹⁷ Low levels of S. epidermidis lead to abnormal proliferation of S. aureus, which may worsen AD symptoms by inducing T-cell proliferation and elaboration of IL-31 and IL-22.¹³,¹⁸ In turn, routine use of antibiotics in AD promotes S. aureus colonization.

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Interestingly, upon clinical improvement with topical treatment, microbial diversity can be reestablished.17

Once AD is established, various other intrinsic and extrinsic factors serve as aggravators of disease, either perturbing an already faulty barrier or provoking inflammatory cascades. Intrinsic factors, such as stress, are hypothesized to trigger release of neuropeptides, such as substance P, which cause neurogenic inflammation. Extrinsic factors, such as excessively arid climates, pollution, food, and personal care products, may lead to hyperinnervation in the epidermis, thereby causing pruritus.20-22 Because of the variety of intrinsic and extrinsic factors that play a role in AD development, the prevalence of AD is higher in certain areas of Africa, eastern Asia, and western and northern Europe.23

### Novel therapies for atopic dermatitis

Therapeutic strategies for AD focus on repairing and reinforcing a defective skin barrier by using emollients and humectants and reversing inflammation by applying topical corticosteroids and calcineurin inhibitors.24 Narrowband or broadband ultraviolet B (UVB), and less commonly UVA, phototherapy may be used in conjunction with topical therapies when individuals have more widespread disease. For severe or refractory AD, use of systemic immunosuppressive agents or immunomodulators such as cyclosporine, mycophenolic acid, and methotrexate may be used. Use of these systemic agents has historically been limited due to their potential side effects, which are more common at the high doses frequently required to control severe disease.25 Newer, more target-ed therapies offer potential for greater disease control with fewer side effects (see Table).

### Phosphodiesterase 4 inhibitors

Phosphodiesterase 4 (PDE4) is an enzyme that degrades cyclic adenosine monophosphate (cAMP) in leukocytes and the central nervous system.26 Elevated levels of PDE4 activity are observed in AD

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**ABBREVIATIONS:** FDA, US Food and Drug Administration; Ig, immunoglobulin; IL, interleukin; JAK-STAT, Janus kinase-signal transducer and activator of transcription; NB, no clear benefit demonstrated; PDE, phosphodiesterase; SC, subcutaneous.
patients and correlate with increased inflammation and decreased barrier function. Inhibition of PDE4 has been used successfully to treat several inflammatory disorders, including AD, psoriasis, asthma, and chronic obstructive pulmonary disease (COPD), resulting in increased cAMP levels in cells with a subsequent decrease in nuclear factor kappa B signaling and cytokine production.26

Topical PDE4 inhibitors include crisaborole, OPA-15406, RVT-501 (E6005), and roflumilast. All of these except roflumilast have demonstrated some efficacy in the management of AD symptoms. In 2 phase 3 trials in pediatric and adult patients with mild-to-moderate AD, the boron-based crisaborole reduced pruritus, erythema, exudation, excoriation, induration or papulation, and lichenification after 28 days.29 In the authors’ experience, a distinct subset of atopic patients shows remarkable improvement with and preference for crisaborole ointment compared with topical corticosteroids and calcineurin inhibitors. The clinical features and genetic susceptibilities that distinguish those patients who respond to crisaborole remain unclear and warrant further study. Application of a 1% formulation of OPA-15406 for 8 weeks relieved symptoms in mild-to-moderate AD patients between 10 and 70 years old.30 In a randomized, investigator-blinded, vehicle-controlled trial in 40 adult male patients, increasing concentrations of topical RVT-501 (E6005) demonstrated improvement in AD lesion severity.31 In contrast to the other PDE4 inhibitors, topical roflumilast failed to demonstrate statistically significant improvement in AD severity.30

The majority of the aforementioned trials were relatively small (40-80 patients), and the effectiveness of these agents must be further evaluated. Adverse events were generally mild, such as application site pain or site infection.27 More severe adverse events included exacerbation of AD, headache, and upper respiratory infection.30 Other topical PDE4 inhibitors, such as LEO29102, GW842470X, and DRM02, completed phase 2 clinical studies in 2010, 2012, and 2014, respectively, but results have yet to be published.27

Oral PDE4 inhibitors are currently approved by the US Food and Drug Administration (FDA) for psoriasis, psoriatic arthritis, and COPD. Apremilast is an oral small-molecule drug that binds the catalytic site of PDE4.32 In one open-label prospective trial, adults with moderate to severe AD achieved at least 50% improvement in their Eczema Area and Severity Index (EASI-50) score within 3 months of initiating treatment with apremilast 30 mg twice daily.33 However, another open-label phase 2 study reported that apremilast was only minimally effective compared with PDE4 inhibition in psoriasis.34 Nausea is the most common adverse event with apremilast and necessitates a slower dose escalation when patients are initially starting the medication.

### Janus kinase-signal transducer and activator of transcription inhibitors

Signaling via the tyrosine kinase family of Janus kinases (JAKs) and signal transducer and activator of transcription (STAT) receptor pathways contributes to the pathogenesis of a growing list of skin diseases and inflammatory disorders, including psoriasis, lichen planus, and AD.35 In AD, multiple growth factors and cytokines have been shown to exert pleiotropic effects via activation of JAK-STAT signaling in different cell types, resulting in increased inflammation due to increased Th2 lymphocyte and eosinophil activity, reduction in regulatory T-cell signaling,36 reduction in keratinocyte production of barrier proteins—including β-defensins and cathelicidins—and induction of itch sensation.37-39 Because of such widespread involvement of JAK signaling, patients with AD may benefit from treatment with small-molecule JAK inhibitors, or JAKinibs.

Tofacitinib, an oral JAK1/3 inhibitor approved by the FDA for treatment of rheumatoid arthritis (RA), has shown promise in reducing inflammation and itch in patients with AD. In a small case series of moderate to severe recalcitrant AD patients, oral tofacitinib therapy decreased body surface involvement and severity of erythema, excoriation, edema or papulation, and lichenification.38 Potential side effects include nasopharyngitis, upper respiratory infections, reactivation of tuberculosis, and herpes zoster.40-43 Laboratory test abnormalities may also arise, including decreased levels of hemoglobin, neutrophils, lymphocytes, and platelets and increased levels of liver transaminases, creatinine, high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), and creatine phosphokinase (CPK).38 No increased risk of malignancy was observed with tofacitinib.42 Of note, these side effect profiles were described primarily in RA patients. In AD patients, no adverse events have been noted, though larger and longer-term studies are needed.44 The authors have used oral and topical formulations of tofacitinib with encouraging results and few side effects in the management of AD-related itch and inflammation, even in patients with severe disease.

Several other oral JAK inhibitors are currently under investigation for efficacy in AD, including baricitinib, PF-04965842, and upadacitinib. In a phase 2 trial comparing the effects of placebo to escalating doses of the oral JAK1/2 inhibitor baricitinib in adult patients with moderate to severe AD, 61% of patients achieved EASI-50 at 16 weeks with 4 mg compared with 57% in those receiving 2 mg and 37% with placebo, resulting in a statistically significant difference between the 4-mg dose and placebo.44 Side effects in these patients included lymphopenia, neutropenia, eczema, and nasopharyngitis.44 No patients had herpes zoster, though that has been a reported side effect previously.42 Although currently approved and available in Europe, FDA approval of baricitinib for use in the United States has been delayed due to the increased risk of thromboembolic disease observed in RA patients. In contrast to RA, there is currently no evidence of increased thromboembolic risk or cancer risk in the atopic population, though longer-term studies are needed.44 In addition, mild laboratory abnormalities have been observed in RA patients receiving baricitinib, including increases in creatinine, liver transaminases, HDL, LDL, and CPK.45-48 Continued use of the agent did not worsen laboratory values nor necessitate discontinuation of the medication.45 Given the distinct pathogenesis and comorbidities of patients with RA, it is difficult to generalize side effects encountered by this patient population to those with AD.

In February 2018, an oral JAK1 inhibitor known as PF-04965842 received breakthrough therapy status from the FDA for treatment of patients with moderate to severe AD. In a phase 2 trial of patients with moderate to severe AD, eczema severity and symptoms significantly improved at 12 weeks compared with placebo.49 Side
effects of the drug were a dose-dependent drop in platelet count and an increase in LDL, HDL, eczema herpeticum, and pneumonia. A phase 3 trial evaluating the efficacy of escalating doses of PF-04965842 in 375 pediatric (12 years of age and older) and adult patients with moderate to severe AD (NCT03349060) is ongoing.

Upadacitinib, another JAK1 inhibitor, demonstrated efficacy in reducing eczema symptoms in patients at the 16-week time point in an ongoing 88-week, phase 2b trial in patients with moderate to severe AD.40 The most common adverse events were upper respiratory tract infection, AD exacerbation, and acne. The long-term safety profile is being evaluated.

Topical JAKinib formulations are also being studied for their role in AD management. Although a phase 2a, 4-week trial reported improvement in AD symptoms with topical tofacitinib,51 topical tofacitinib has failed to progress further at this time.40 The topical JAKinib JTE-052, which targets JAK1/2/3 and tyrosine kinase 2, improved EASI scores at 4 weeks and was well tolerated in adults with moderate to severe AD.49 Results from this study may include nasopharyngitis, improved EASI scores at 4 weeks and was well tolerated in adults with moderate to severe AD.49 Results from this study may be limited, however, because of the short duration, small sample size, and open-label design. A topical form of ruxolitinib, an oral JAK1/2 inhibitor approved by the FDA to treat hematological diseases, is currently under investigation in a phase 2 trial for AD (NCT03011892).

Given the broad and potent nature of their effects, as well as their small-molecule design lending itself to oral therapy, JAKinibs represent a promising therapy for patients with moderate to severe AD. Nonetheless, their potential side effects and safety profile will need to be considered on an individual basis, similar to present-day use of cyclosporine.

**Anti-IL-4 and IL-13 therapy**

Dupilumab is a fully human immunoglobulin (Ig)G4 monoclonal antibody against the shared IL-4 receptor alpha (IL-4Rα) subunit of IL-4 and IL-13, 2 key cytokines that drive the type 2 inflammatory response. Dupilumab is thought to work by reversing inflammation and correcting skin barrier defects.32 IL-4 and IL-13 have also been shown to directly activate itch signaling in animal models, suggesting another method by which dupilumab may benefit patients with AD.7 In March 2017, dupilumab was approved by the FDA for treatment of AD that is inadequately controlled by topical prescriptions or when those therapies are contraindicated.

Early-phase trials of dupilumab versus placebo in adult patients with moderate to severe AD with eosinophilia showed marked reduction in symptoms and Th2-associated biomarker levels.53 Phase 2b randomized trials confirmed these findings.34 More recently, 2 randomized, placebo-controlled phase 3 trials of identical design (SOLO 1 and SOLO 2) compared dupilumab monotherapy to placebo and found that patients who received subcutaneous dupilumab (300 mg) every other week were 3 to 4 times more likely to achieve a reduction in investigator global assessment score to clear or almost clear and at least a 75% improvement in baseline EASI score at week 16 compared with placebo.54 Longer-term trials found that dupilumab remains effective after 1 year of therapy and has an acceptable safety profile.56 Dupilumab decreases use of rescue treatments and provides long-term benefits in patient-reported outcomes, such as anxiety and depression, with significant improvements in pruritus occurring as early as week 2.57 In our clinical practice, complete or near complete clearance occurs in approximately 25% of patients on every-other-week dosing of dupilumab and in 30% to 35% with weekly dosing (in contrast to rates of 36%-38% of patients reported as clear or near clear with every-other-week dosing in the SOLO 1 and 2 trials). In the authors’ experience, approximately 60% of patients experience a partial reduction in dermatitis and symptoms (itch, pain, and burning), often with areas of residual disease affecting special sites (eg, acral surfaces, scalp, genitalia) or areas of previously severe involvement. In some cases, patients have little to no improvement. While this represents huge strides in the management of AD, determining which patients will respond optimally to dupilumab and understanding why those who fail do so are critical next steps.

The most common adverse events reported in dupilumab trials included nasopharyngitis and injection site reactions, while more severe events include increased susceptibility to herpes viral infections.45-56 Rates of conjunctivitis ranged from 3% to 7% in phase 2 and 3 studies53,55; however, some reports, as well as the authors’ experience with dupilumab, suggest that conjunctivitis affects closer to 15% of patients or more.56 In most patients with ocular symptoms, individuals may continue on the biologic but require saline lubricant drops or ophthalmic steroid preparations to reduce symptoms. In the authors’ experience, only a small number of patients have needed to discontinue dupilumab entirely despite attempts to control conjunctivitis. Interestingly, the rate of conjunctivitis is not higher in asthmatic or nasal polyposis patients on dupilumab, suggesting that there are characteristics of AD that contribute to conjunctivitis.58-60

Patients treated with dupilumab had reduced incidence of non-herpetic skin infections, possibly due to restoration of skin barrier, reduced scratching, or improved antimicrobial or innate immune responses.53 In addition, there were comparable rates of infection in treatment and placebo groups.55,56 Dupilumab might be the first targeted immune biologic that is neither immunosuppressive nor associated with increased risk of infection.55,56

In general, further studies examining the long-term effects of dupilumab and dupilumab’s efficacy in the pediatric population, as well as comparator studies with alternative systemic agents, must be performed. There is currently a trial of dupilumab in children and adolescents, with preliminary studies demonstrating efficacy in patients 6 to 18 years old (NCT02407756). Another phase 2/3 trial of dupilumab in children younger than 6 years of age is currently recruiting (NCT03346434).

**Anti-IL-13 therapy**

IL-13 drives type 2 inflammation and contributes to AD pathogenesis. IL-13 is up-regulated in AD patients, and levels have been shown to correlate with disease severity.51-62 In animal models, overexpression of IL-13 down-regulates skin barrier proteins63,64 and is associated with direct stimulation of itch.7 Lebrikizumab and tralokinumab bind IL-13, thereby preventing IL-13 from binding to IL-4Rα and limiting downstream effects of this cytokine.

After promising results in asthma,65 a phase 2b trial evaluating the efficacy of lebrikizumab in adults with moderate to severe AD found that significantly more patients receiving interval dosing of
lebrikizumab (82.4%) achieved EASI-50 at 12 weeks than those receiving placebo (62.3%). A caveat was that patients had to be on lebrikizumab every 4 weeks to experience effect; patients who received a single dose had no improvements in AD symptoms compared with placebo. Lebrikizumab was generally well tolerated, with adverse events affecting approximately 66% of participants in both treatment groups. Increased peripheral blood eosinophil counts have been observed with lebrikizumab and have been attributed to decreased eosinophil trafficking from the blood to the airways as a result of reduced chemotaxis in the setting of IL-13 blockade.

In a separate phase 2b study blocking IL-13 signaling with the human Ig4 monoclonal antibody tralokinumab, adults with moderate to severe AD had a significant reduction in EASI scores and other severity outcomes when treated with tralokinumab 150 mg or 300 mg subcutaneously every 2 weeks compared with placebo, and improvement in quality of life and reduced S. aureus colonization at the 300-mg dose. Study participants in all arms of this study were able to use topical corticosteroids, which may influence interpretation of the efficacy and high placebo response rate. The most frequent adverse events were nasopharyngitis, upper respiratory tract infection, headache, and AD. This drug is currently undergoing a 32-week phase 3 trial (NCT03363854).

Efficacy of treatment with IL-13 inhibitors (eg, lebrikizumab and tralokinumab) versus combined IL-13 and IL-4 blockade (eg, dupilumab) may provide insight into the relative importance of these cytokines to AD pathogenesis. Both share overlapping biology and effector functions, and it remains unclear at this time whether inhibition of IL-13 alone will provide equally effective treatment for AD—due to its more targeted mechanism—as well as in which individuals this may be a reasonable therapy.

**Anti-IL-31 therapy**

IL-31, a Th2 cytokine, has been implicated in several aspects of AD pathogenesis, including functioning as a major pruritogen, disrupting epidermal terminal differentiation, and enhancing inflammatory cytokine elaboration. IL-31 enhances the synthesis and release of a central itch mediator known as brain-derived natriuretic peptide in DRG neurons and in the skin, and it influences cytokine release within the skin. Nemolizumab is a humanized monoclonal antibody that antagonizes the IL-31 receptor A on keratinocytes and monocytes. In a phase 2 double-blind, placebo-controlled trial, patients with moderate to severe AD who received subcutaneous nemolizumab at increasing doses (0.1 mg, 0.5 mg, and 2 mg per kg of body weight) demonstrated a dose-dependent reduction in pruritus and eczema severity at 12 weeks compared with those receiving placebo. Adverse events included exacerbations in AD and peripheral edema, but nemolizumab was tolerated well overall. Although promising, larger placebo-controlled clinical trials will be required to determine what role nemolizumab may play in the AD therapeutic landscape.

**Anti-IL-12 and IL-23 therapy**

Ustekinumab is a human monoclonal antibody that targets the p40 subunit of IL-12 and IL-23. IL-12 triggers proliferation of interferon gamma, T cells, and natural killer cells, whereas IL-23 is involved in the differentiation of Th17. Ustekinumab has been successfully used in chronic plaque psoriasis, but a role for this mechanism in treating AD is less clear. In one promising, double-blind crossover phase 2 trial comparing ustekinumab to placebo over 32 weeks in 33 patients, clinical improvement in AD severity and normalization in several molecular cytokines and markers of epidermal hyperplasia was observed; however, these changes failed to meet significance. Lack of statistical significance between treatment and placebo arms may reflect the concomitant use of topical steroids or that the drug was underdosed for the atopic population compared with patients with psoriasis. In one case report of 2 patients, atopic disease was either not controlled or rebounded several months into treatment with ustekinumab. Similarly, 2 patients with psoriasis well-controlled with ustekinumab suffered atopic flares during their treatment course. A systematic review of ustekinumab for AD concluded that of 54.2% of patients receiving the drug, that were reported in individual cases or in clinical trials, showed some improvement in disease. Given these mixed reports, it is possible that Th17 plays a larger role in certain subpopulations with AD, eg, those with intrinsic AD or in Asians in whom Th17 activation may play a more prominent role in disease pathogenesis.

**Anti-IL-17A therapy**

Secukinumab is a fully human monoclonal antibody directed against IL-17A that is approved for moderate to severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. IL-17A is produced by Th17 cells, stimulates Th2 responses in acute AD, and is elevated in AD lesions and peripheral blood. Although targeting IL-17A to treat AD may be helpful, it is currently unknown what effects and potential adverse events may be seen in the atopic population. A phase 2, placebo-controlled randomized clinical trial is currently underway (NCT02594098) to determine the safety and efficacy of IL-17A inhibition in AD patients.

**Anti-IL-22 therapy**

Fezakinumab (ILV 094) is a fully human monoclonal antibody directed against the cytokine IL-22. IL-22 induces epidermal hyperplasia while inhibiting proteins involved in epidermal differentiation and ultimately contributes to epidermal barrier dysfunction. A randomized, double-blind, placebo-controlled phase 2a clinical trial reported that intravenous fezakinumab delivered every 2 weeks over 10 weeks reduced AD severity, although the mean change in AD severity failed to meet statistical significance. In adults with severe AD baseline, significant improvement was observed in body surface area involvement and investigator global assessment scores at 12 weeks. Adverse events occurred with similar frequency in treatment and control groups, with the most common being viral upper respiratory infections. While these results suggest that IL-22 antagonism may be useful in the management of severe cases of AD, additional studies will be required to determine long-term safety and efficacy in this patient population.
Anti-IgE therapy

Omalizumab is a humanized IgG1 monoclonal antibody that binds IgE and inhibits mast cell and basophil activation. A meta-analysis of multiple case series and 2 randomized controlled clinical trials found omalizumab ineffective for AD, though potential benefits might be seen in patients with lower IgE serum concentrations.90 IgE antagonism may not be an effective method to combat atopic disease because Th2 plays a role in IgE class switching, but not in inflammation per se.91 Interestingly, altered lipid profiles with disease because Th2 plays a role in IgE class switching, but not in inflammation per se.91 Interestingly, altered lipid profiles with elevated glycerophospholipids and the absence of FLG mutations in patients with AD correlate with a better clinical response to omalizumab.92 The impact of these observations on the use of omalizumab in AD remains unclear, and larger randomized controlled trials would be required to determine whether subpopulations of AD patients may benefit from single or adjuvant use.

Conclusions and caveats

More than a decade passed between the approval of tacrolimus ointment for the treatment of AD in 2006 and the first AD biologic dupilumab in 2017. During this apparent lull, our understanding of the pathogenetic mechanisms of AD expanded dramatically, and the medical community is now on the verge of a virtual explosion of treatment options to manage this challenging disease. Just as biologics have revolutionized psoriasis treatment and improved quality of life, these newer therapies hold tremendous promise for influencing disease severity and quality of life impact in AD. In the current pipeline are various topical, oral, and injectable therapies that target distinct cytokines and molecular pathways that lead to the inflammation and/or itch that drives AD. Thus far, anti-Th2 cytokine antagonists and JAKinibs hold tremendous promise for patients with moderate to severe AD. However, it is important to recognize that, while these agents may improve AD severity or symptomology without the exact side effects of traditional systemic immunosuppressive agents (eg, cyclosporine, mycophenolate, etc.), they do not come entirely without risks, and managing the potential side effects (eg, conjunctivitis with dupilumab) may prove challenging. Long-term safety data are needed to evaluate potential sequelae from these novel targeted therapies, particularly with respect to JAKinibs. Given their diverse cellular distribution and downstream functions, JAKinibs may be viewed in some respects as broadly acting as current immunosuppressive agents.

Many of the trials summarized earlier were limited due to use of concomitant topical corticosteroids, short study duration, and insufficient study size to detect significant differences between groups. Large placebo effects were also observed, potentially reflecting improved adherence to a treatment regimen, the palliative nature of emollients, and concomitant topical steroid use. It is also important to recognize that AD is a heterogeneous disease. Current studies only stratify based on disease severity and not other patient characteristics. For example, recent trials focused primarily on adults with AD, although trials in pediatric populations are now underway for select agents. Subgroup analysis to identify the role of age, race/ethnicity, disease comorbidities, and/or other genetic susceptibilities in therapeutic responses will provide useful information when developing informed treatment algorithms. As the therapeutic armamentarium for AD grows, head-to-head comparisons of novel treatments with current first-line therapy will also need to be evaluated.

References


49. Kim BE, Leung DY, Boguniewicz M, Howell MD. Loritcin and involucrin ex-


