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Atopic dermatitis: emerging therapies

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■ **Abstract**

Crisaborole and dupilumab represent the first 2 Food and Drug Administration (FDA)-approved therapies for atopic dermatitis (AD) in more than 15 years, and there are many promising drugs currently in development. This new wave of therapeutics capitalizes on the large body of work clarifying the pathogenesis of AD over the last several decades. In particular, type 2 cytokine-driven inflammation and skin barrier dysfunction are key processes underlying AD pathogenesis.

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Atopic dermatitis (AD) is a disease of both altered immunity/inflammation and barrier dysfunction.[1,2] Current medical therapies for AD address primarily the inflammatory features of the disease. Nevertheless, skin care and emollients do improve skin barrier function and reduce disease flares and can even be an effective prevention strategy. The treatment of AD inflammation includes the use of topical corticosteroids (TCS) as first-line therapy with topical calcineurin inhibitors (TCI) serving as second-line therapy at sites where TCS use may be ill-advised. There are several potential limitations to TCS treatment when used for widespread, severe disease, including local and systemic toxicities such as development of telangiectases and skin atrophy, and risks of adrenal suppression, growth retardation and ocular cataracts.[3] TCI use is commonly associated with initial burning and stinging, and as a class they carry a Food and Drug Administration (FDA)-issued boxed warning because of rare malignancies reported with their use. Many independent groups and substantial post-marketing data have argued, however, that the black box warning is unfounded.[4]

Moderate to severe AD not adequately controlled with appropriate amounts of topical therapy is treated with phototherapy or systemic immunosuppressive medications such as cyclosporine, methotrexate, mycophenolate and azathioprine. While studies show a beneficial effect for these medications in AD, their use is limited by modest efficacy (eg, azathioprine, mycophenolate) or the potential for end-organ toxicity (eg, cyclosporine or methotrexate) with long-term use. Because of their ease of use and low cost, systemic steroids are the most commonly prescribed systemic therapy used for AD despite their well-known adverse side effects.

Given the limitations of these traditional topical and systemic therapies in AD, a large unmet need remains. Novel topical and systemic therapies for the safe and effective long-term management of AD are greatly needed. In the remainder of this paper, we will review newly-approved and emerging topical and systemic medications for AD as well as novel early life approaches to preventing the disease onset.

Early therapy and AD prevention

Barrier repair

Recent investigations reveal that interventions to prophylactically repair the epidermal barrier may prevent or delay the onset of AD. The Barrier Enhancement for Eczema Prevention (BEEP) pilot study, performed by Simpson and colleagues, studied the efficacy and feasibility of early prophylactic use of emollients in

high-risk patients.[5] The study examined 124 infants younger than 3 weeks old. One study arm utilized an oil or bland emollient and skin care advice while the control group received only skin care advice. They reported a 50% reduction in AD development in the emollient group at 6 months of age with no differences in adverse events between the emollient and untreated groups. A comparable Japanese study of neonates at high risk for AD who received daily moisturizer during the first 32 weeks of life, found that they were 32% less likely to develop eczema or AD compared with those in the control group.[6] Currently, larger trials are being conducted to confirm these encouraging findings and assess their durability. Given the high prevalence of pediatric AD (up to 20% in the United States),[7] even a 20%-30% reduction in disease prevalence would have major implications for public health. Additionally, AD is often seen as the initial disease that is followed by other atopic diseases such as food allergy and asthma.[8] One hypothesis for this association purports that skin barrier disruption promotes IgE sensitization, thus barrier enhancement may reduce allergen sensitization.[2] Support for this notion comes from an Irish birth cohort study that demonstrated that healthy infants with the greatest degree of skin barrier dysfunction were more likely to develop atopic dermatitis and food allergy.[9,10] Studies are underway to evaluate whether skin barrier protection and reducing the risk of AD could have positive effects on a child's risk of additional allergic comorbidities.

Probiotics

The use of probiotics and their benefits for AD have been a hotly debated topic within the medical literature. Similarly, probiotics have had mixed effects in the field of AD. Accumulating evidence supports that probiotics exert their effects by activating pattern recognition receptors, such as toll-like receptors, to produce downstream effects such as modulation of the nuclear factor-Kappa B pathway,[11] suppression of interleukin (IL)-4 and thymic stromal lymphopoietin (TSLP) production, and altering the composition of gut flora.[12] Probiotics have been studied for both prevention and treatment of AD.

A recent meta-analysis of randomized controlled trials (RCT) found that probiotic use significantly reduced the risk of infants developing eczema when used by women during the last trimester of pregnancy, with a relative risk (RR) of 0.71 (95% confidence interval [CI], 0.60-0.84).[13] Additionally, the meta-analysis found a RR of 0.57 (0.47-0.69) when probiotics were used by breastfeeding mothers and a RR of 0.80 (0.68-0.94) when given directly to infants. The World Allergy Organization recommends probiotics for AD prevention but states, "All recommendations are conditional and supported by very low quality evidence." In regards to probiotics for the treatment of AD, the most recent meta-analysis found only slight reductions in AD severity in children and adults, and borderline clinically relevant effect sizes.[14]

Dust mite avoidance

A recent systematic review and meta-analysis of dust mite avoidance performed by Bremmer and Simpson examined 7 RCTs and included a total of 3040 subjects.[15] They found that dust mite avoidance provided no benefit in the prevention of AD (RR = 1.08; 95% CI, 0.78-1.49). Similarly, there was little evidence to support the use of dust-mite avoidance for the treatment of established AD,[16] and current guidelines do not promote the use of dust mite-reducing products in this manner.[17]

Hydrolyzed formula

Hydrolyzation of infant formula to reduce the size and molecular weight of bovine peptides (particularly whey and caseins) has been proposed to decrease potential sensitization to allergens that may purportedly lead to the development of AD.[18] However, the deliberate introduction of hydrolyzed formula is controversial as there are many studies to both support[19,20] and refute this hypothesis.[21] Although further studies are required, hydrolyzed infant formulas may be a cost-effective method for the primary prevention of AD.[18] The FDA has allowed a qualified health claim in favor of hydrolyzed formula for use in healthy infants with a family history of allergy from birth to 4 months of age who are not exclusively breastfed. It states that the use of partially hydrolyzed whey protein formula, instead of a formula containing intact cow's milk proteins, may reduce the risk of developing AD.[22] The most recent meta analysis, however, did not find strong enough evidence to support hydrolyzed formula of any type for AD prevention.[21]

New and emerging pharmaceuticals for AD treatment

PDE-4 inhibitors

In the mid-1990's, Hanifin and colleagues demonstrated inhibition of phosphodiesterase (PDE), an intracellular enzyme present in several immune cells, reduced levels of Th2-cell driven pro-inflammatory cytokines such as IL-4.[23] PDE-4 inhibitors are thought to increase intracellular cyclic adenosine monophosphate (cAMP) and decrease the leukocyte inflammatory response by suppressing interferon-gamma, tumor necrosis factor, and interleukin-4, 5, and 13 production, potentially abrogating the inflammatory response in AD.[24,25] Topical and systemic PDE-4 inhibitors were pursued, but initial agents either showed little effect topically or had too much gastrointestinal toxicity systemically. Newly-developed inhibitors can now better target PDE-4 with fewer off-target toxicities.

Eleven families of PDE enzymes have been identified and each has a different selectivity profile. While PDE-4 selectively inactivates cAMP, PDE-2 is thought to inactivate cAMP and cyclic guanosine monophosphate (cGMP).[26] Multiple PDE inhibitors are currently being tested, and manufacturers have made claims to the superiority of their product based on its potential PDE inhibitor selectivity. However, there is insufficient data now to support these claims.

Crisaborole

Crisaborole is a topical PDE-4 inhibitor. As a small molecule, it has good skin penetration and the boron-based architecture contributes to molecular stabilization.[27] Crisaborole is a non-steroid pharmaceutical and is not associated with the side effects of topical corticosteroids (TCS) such as telangiectasia and skin atrophy. Crisaborole's safety was demonstrated in AD subjects 2 years and older in a phase Ib trial and 2 phase II clinical trials.[28-30] Mild application site pain and nasopharyngitis were reported side effects, but no serious or severe reactions were reported in these trials.

Two identically designed phase III clinical trials studying 1522 subjects (1016 received crisaborole and 506 received vehicle) confirmed the efficacy and safety of crisaborole therapy.[31] Crisaborole ointment was applied twice daily for 28 days in subjects 2 years and older with mild (Investigator's Static Global Assessment [ISGA] score of 2) to moderate (ISGA of 3) AD. A 2-grade or greater improvement in ISGA score to clear (0) or almost clear (1) skin was the primary end-point. Disease severity was quantified using pruritus, erythema, excoriation, exudation, induration or papulation, and lichenification scores—not a standardized AD severity scale such as the SCORing Atopic Dermatitis (SCORAD) or the Eczema Area and Severity Index (EASI) scores. A significant improvement over placebo in ISGA score and disease severity was noted as early as day 8 in the crisaborole ointment group. The only statistically significant adverse effect of crisaborole therapy was application site pain found in 4.4% of the crisaborole group and 1.2% of vehicle-treated subjects (P = .001). However, most subjects had resolution of this adverse effect within 1 day of onset.

Crisaborole's long-term safety was later demonstrated in an open-label, 48-week trial performed by Eichenfield and colleagues.[32] They administered multiple 28-day cycles of crisaborole were administered as needed to more than 500 patients. No attributable serious adverse events were noted during this trial, but application site burning was present in 2.3% of subjects. A recent vehicle-controlled study by Zane and colleagues demonstrated that crisaborole application to sensitive areas was well tolerated as vehicle.[33]

The FDA approved crisaborole for use in subjects 2 years and older with mild to moderate AD in the fourth quarter of 2016. This was the first alternative topical treatment of AD to be approved by the FDA more than 10 years. Theoretically, crisaborole could be used as first-line therapy for mild to moderate AD, but the advantages over appropriately used and inexpensive mild- to moderate-potency TCS would need active comparator trials to elucidate, especially given the significant cost of crisaborole over currently available TCS options. Furthermore, head-to-head studies with TCIs would also help determine what role crisaborole has in the current non-steroidal treatment paradigm.

MM36

MM36 is a topical PDE-4 inhibitor that completed a phase II clinical trial. Hanifin and colleagues recruited 121 subjects from 10 to 70 years old with mild to moderate AD and randomized them to either a 0.3% or 1% MM36 (previously known as OPA-15406) ointment or to vehicle twice-daily for 8 weeks.[34] At 1week, a 31.4% improvement in mean EASI scores, versus 6.0% in vehicle, was noted in the 1% MM36 arm and continued to improve through week 8. Smaller treatment effects were observed in the 0.3% MM36 group (P = .0005). Five-point Investigator's Global Assessment (IGA) scale (0 = clear to 4 = severe) scores improved in the 1% MM36 treatment group with minimal change in the other 2 groups. The rate of adverse events was similar for both treatment groups and vehicle, and no severe reactions occurred.

RVT 501

RVT 501 is yet another novel, PDE-4 inhibitor in development that completed a phase II RCT of 81 subjects. The effects of incremental RVT 501 (previously E6005) concentrations from 0.01 to 0.2% applied over a 10-day period were assessed. They observed an overall dose effect, and there was a clinically significant decrease in EASI and SCORAD scores in the 0.1% and 0.2% groups compared with vehicle.[35]

Dupilumab (IL-4/13)

Dupilumab is a novel, subcutaneously administered therapy for AD that targets the IL-4 receptor alpha subunit that is shared between both IL-4 and IL-13 receptors. A phase IIb RCT was performed by Thaçi and colleagues to examine various regimens of dupilumab dose over a 16-week period.[36] In total, 380 subjects with active moderate to severe AD, despite the use topical therapies were randomized into various therapeutic and placebo arms of the trial. The group with the highest dose (300 mg per week) experienced a 73% improvement in EASI score, while the lowest dose (100 mg every 4 weeks) had a 44% EASI improvement. There was a similar rate of treatment-emergent adverse events in the placebo and dupilumab groups. There was an increase in herpes simplex virus infections in the dupilumab groups (8%) compared with the placebo group (2%).

The promising results of these earlier phase studies were then retested in larger phase 3 pivotal trials named SOLO1 and SOLO2. These identically designed trials included 1379 subjects with moderate to severe AD that was not adequately controlled with topical therapies or who were not able to tolerate topical medications. An IGA score of 3 or 4 (moderate to severe) was part of the inclusion criteria and an EASI score was calculated at baseline. The subjects received either placebo for 16 weeks or a 600 mg loading dose of dupilumab followed by either 300 mg dupilumab once weekly (qw) or every 2 weeks (q2w). The 300mg qw groups in the SOLO1 and SOLO2 trials had 37% and 36% of subjects, respectively, achieve clear or almost clear IGA scores (clear = 0, almost clear = 1). In the 300 mg q2w group, an IGA of 0 or 1 was achieved in 38% and 36% of subjects for the SOLO1 and SOLO2 trials, respectively. In contrast, the placebo groups achieved an IGA of 0 or 1 in 10% of SOLO1 subjects and only 8.5% of SOLO2 subjects. AD signs severity was also significantly decreased in the dupilumab arms compared with placebo (P < .0001). The EASI improvement over baseline was 72% and 69% in the 300mg qw group, 72% and 67% in the 300mg q2w group, and 38% and 31% for placebo in the SOLO1 and SOLO2 trials, respectively.

Several other clinical endpoints important to patients with AD were measured, such as average peak itch intensity, general AD symptoms as measured by the Patient-oriented Eczema Measure (POEM), quality of life (QOL), and mental health symptoms. Dupilumab treatment led to significant improvement in all of these endpoints with effect sizes exceeding what constitutes a clinically meaningful benefit, including measures of overall health and well-being.

The overall rate of adverse events was similar in both the placebo groups (65% and 72%) and the dupilumab groups (65% and 75%) in both trial arms. In fact, a lower incidence of adverse events was seen in the dupilumab groups (1% and 3%) compared with the placebo groups (5% and 6%). However, injection site reactions and conjunctivitis were more commonly observed with dupilumab therapy. Herpes infections did not vary between treatment groups,

as was observed from earlier, smaller studies.

An additional phase III RCT, named LIBERTY AD CHRONOS, examined the long-term safety and efficacy of dupilumab therapy when used with concomitant topical therapy.[37] A total of 740 subjects were randomly assigned into dupilumab 300 mg qw (319 subjects), dupilumab 300 mg q2w (106 subjects), or placebo (315 subjects) groups. Subjects could concurrently use TCS as needed in both the treatment and placebo groups throughout the study. At 16 weeks, significantly more subjects receiving dupilumab qw and q2w groups achieved an IGA score of 0 or 1 (39% and 39%) compared with the placebo group (12%, $P < .0001$). A 75% reduction in EASI score (EASI-75) was also more commonly achieved in both dupilumab groups (64% and 69% respectively) compared with the placebo group (23%, $P < .0001$).

At 52 weeks, a total of 623 subjects remained in the trial—85% of the dupilumab qw, 86% of dupilumab q2w, and 67% of the placebo group. The results at 52 weeks were similar to those at 16 weeks and a significant proportion of subjects in both the dupilumab qw (40%) and q2w (36%) maintained an IGA score of 0 or 1 compared with the placebo group (13%, $P < .0001$). In addition, the proportion of subjects who achieved an EASI-75 was also significantly different ($P < .0001$) between the placebo (22%) and the dupilumab qw (64%) and q2w (65%) groups. Higher rates of non-herpes viral skin infections were observed in the placebo group (18%) compared with the dupilumab qw (8%) and q2w (11%) groups. The dupilumab qw and q2w treatment groups had a higher proportion of injection site reactions (19% and 15%) and conjunctivitis (19% and 14%) compared with placebo (8% and 8%). However, no clinically significant laboratory abnormalities were associated with dupilumab therapy.

Overall, phase 3 studies reveal dupilumab therapy provides clinically meaningful improvement in multiple dimensions of health for patients with AD including signs, symptoms, quality of life, and mental health comorbidities. Dupilumab safety up to 1 year appears favorable with only injection-site reactions and conjunctivitis emerging as side effects. No laboratory monitoring is required. Dupilumab is only the second systemic drug FDA-approved for the treatment of AD (after oral corticosteroids) and provides new hope for our long-suffering patients with AD.

Anti-Interleukin- 13 antagonists

The spectrum of Th2 cell-derived cytokines such as IL-4, IL-5, and IL-13 are very important to the pathogenesis of AD and are associated with IgE sensitization.[38,39] The role of IL-13 in AD pathogenesis is well understood, and novel therapies attempt to deactivate these pathways in both AD and asthma. IL-13 causes dysregulation of epidermal barrier proteins by downregulating filaggrin, loricrin, and ivolucrin.[40] IL-13 also strongly stimulates transient receptor potential ankyrin 1 (TRPA1), thereby evoking the itch response.[41] In addition, IL-13 enhances airway remodeling in asthma through its stimulating effects of goblet cells, bronchial fibroblasts, and airway smooth muscle cell.[42] While dupilumab targets IL-13 in addition to IL-4 receptors, lebrikizumab and tralokinumab are IL-13-specific inhibitors. Lebrikizumab is currently in phase III clinical trials for AD while tralokinumab is in phase II clinical trials.

Antipruritic agents

Itch has a large impact on patients' quality of life and is as an essential feature to be included in many objective atopic dermatitis severity scales.[43] New therapeutic agents are being developed to target pruritus, regardless of direct mechanistic impact on the clinical signs of AD.

Anti-Interleukin-31 receptor antagonists

Activated Th-2 cells secrete IL-31 (or "pruritus-specific interleukin"), which is thought to play a large role in the pruritus observed in AD and may be associated with disease progression.[2] Nemolizumab is an IL-31 inhibitor that has completed a 12-week phase II RCT with promising results.[44] During this dose-finding trial, subjects between 18 and 65 years old with AD inadequately controlled with topical therapies, were randomized to receive 0.1mg, 0.5 mg, or 2.0 mg nemolizumab per kilogram body weight once every 4 weeks, 2.0 mg of nemolizumab once every 8 weeks (an exploratory arm), or a placebo control. The primary endpoint of the study was a reduction in pruritus on a visual analogue scale (VAS). Patients were not allowed to continue using TCS or TCI during the study; however, patients who had no improvement on the pruritus (VAS) by week 4 were permitted to use potent TCS rescue therapy. There was a significant ($P < .01$) reduction in pruritus for those in the 0.1mg (-43.7%), 0.5 mg (-59.8%), and 2.0mg (-63.1%) groups compared with the placebo control (-20.9%). Changes in the EASI score were a secondary endpoint and were −23.0%, −42.3%, and −40.9%, in the 0.1 mg, 0.5 mg, and 2.0 mg groups respectively, versus −26.6% in the placebo group.

The total number of adverse events was similar in both the placebo and nemolizumab groups. However, serious adverse reactions in the 2.0 mg per kilogram every 4 and every 8 weeks nemolizumab groups included 2 subjects with peripheral edema (1 and 1, respectively) and 3 subjects with AD-related adverse effects (2 and 1 respectively) as compared with no serious adverse reactions in the placebo group. Nemolizumab continues to be a promising emerging therapy that will likely enter phase III clinical trials in the near future.

CT327

CT327 has been shown to inhibit capsaicin responses in sensory neurons and improve itch in psoriasis.[45] This topical agent is being examined in AD and has completed a phase II clinical trial (NCT01808157), but results from this trial are not yet available.

Neurokinin 1 receptor (NK1R) Antagonism

NK1R antagonists are thought to have potential in treating the AD-associated pruritus through reducing the stimulatory effect of substance-P on the neurokinin-1 receptor in the peripheral skin, nerve endings, and possibly the brain.[46-48] Aprepitant is an oral NK1R antagonist that approved by the FDA as an antiemetic drug, but is also effective in managing the pruritus associated with Sezary syndrome[49] and prurigo nodularis.[46] It and other NK1R antagonists (such as tradipitant)[50] are specifically being tested in subjects with AD. However, the role of NK1R antagonists in AD therapy is still unclear.

Kappa-opioid receptor agonists

Kappa-opioid receptor (KOR) agonists also play an important role in the transmission of itch and pain from the skin to the brain and act on the central nervous system to reduce pruritus.[50,51]

Asimadoline is an oral KOR agonist in phase II AD trials that is being developed to exploit this pathway in hopes of reducing pruritus.

Mixed lipid therapy

A novel oral mixed lipid therapy called DS107 recently completed an 8-week phase II RCT with positive results (NCT02864498). Preliminary data were posted on the company website.[52] They indicated that 21.6% of subjects from the intent-to-treat analysis receiving DS107 achieved an IGA 0/1 compared with 11.8% of controls. Mild nausea, abdominal pain, and/or loose stools caused one-quarter of subjects to either interrupt or discontinue participation in the trial. However, these adverse events were equally common in the placebo group. The active ingredient in DS107 is dihomo gamma linolenic acid (DGLA), a fatty acid with endogenously produced, anti-inflammatory metabolites. DGLA is thought to be deficient in AD skin and replenished by oral supplementation.

Histamine 4 receptor antagonism

Though Histamine (H)-1 receptor blockers are not effective in managing the pruritus of AD, H4 receptors are thought to mediate histamine-induced pruritus and inflammation, and are being investigated to control the pruritus of AD.[53] ZPL-389 is an oral H4 receptor antagonist that was recently studied by Werfel and colleagues in a phase IIa proof of concept RCT.[54] Subjects with moderate to severe AD between 18 to 65 years old were randomized to either ZPL-389 (65 subjects) or placebo (33 subjects) for 8 weeks. The ZPL-389 group experienced a mean 50% reduction in EASI score compared with a 27% mean reduction in the placebo group (P = .01). In addition, 19% of subjects receiving ZPL-389 achieved an IGA of 0/1, while only 9% of subjects receiving placebo had a similar response. The authors reported that ZPL-389 was well tolerated, and the number of adverse events was similar in both the placebo and ZPL-389 groups.

Liver X receptor beta antagonism

Liver X receptor beta (LXR-Beta) was recently proposed as a potential therapy for AD, as it displayed some efficacy in murine models.[55] However, a phase II RCT of VTP-38543, a LXR-Beta inhibitor, did not find supportive results.

Janus kinase inhibitors

Many cytokines, such as IL-4, IL-13 and IL-31 utilize the Janus Kinase (JAK) and Signal Transducer and Activator of Transcription (STAT) signal transduction pathway. Tofacitinib is an oral small molecule JAK 1/2 inhibitor that has been shown to directly inhibit these cytokines and reduce inflammation.[56] A phase IIa RCT[57] had subjects from 18 to 60 years old with mild to moderate AD apply either 2% tofacitinib ointment or vehicle for 28 days. There was a significant improvement in pruritus by day 2 with tofacitinib and an improvement in EASI and physician's global assessment (PGA) scores by week 1. Mild to moderate infections (including nasopharyngitis, upper respiratory tract infection, etc) occurred in 6 tofacitinib-treated subjects and 3 subjects who received vehicle. Unexpectedly, application site reactions were more common with vehicle. A case series showing beneficial effects with oral tofacitinib hint at the promise of oral JAK/STAT inhibition for severe AD.[58] Other JAK inhibitors are under investigation for atopic dermatitis and other inflammatory skin conditions.

Chemoattractant receptor-homologous molecule 2 antagonism

Stimulation of the chemoattractant receptor-homologous molecule (CRTH2)-transmembrane prostaglandin D2 receptor that is expressed on Th2 lymphocytes leads to cell activation and chemotaxis.[59] Q301 is a topical cream thought to antagonize the CRTH2 receptor and decrease the Th2 response in AD. A phase II RCT that compared twice-daily Q301 to vehicle in subjects with moderate to severe AD over 8 weeks was recently completed (NCT02426359), but the study results have not been published.

Microbial therapies

Although largely unproven, *Staphylococcus aureus* colonization has been proposed as a mechanism for both AD progression and exacerbation.[60] A recent state-of-the-art investigation by Nakatsuji and colleagues showed that amplification and autologous transplantation of coagulase negative Staphylococci that produce anti-*S. aureus* peptides resulted in decreased *S. aureus* colonization.[61] This concept is currently being built upon, and a phase II clinical trial (NCT02144142) is being conducted.

Conclusion

The number and breadth of new and more targeted therapeutics for the prevention and treatment of AD has exploded after almost 20 years of stagnancy since the approval of TCIs for AD. There is a large unmet need for treatment options for AD patients who are refractory to currently available topical medications and/or who desire corticosteroid-free alternative therapies. The therapeutics currently under development are designed to fill these niches; however, despite their number, many of these novel therapies may not be available for AD patients because of toxicities, poor efficacy, costs, or lack of studies in pediatric populations. New systemic and topical therapies such as dupilumab and crisaborole, are already available for clinical use and more novel therapeutics are anticipated soon. These targeted therapies will hopefully change AD treatment paradigms and lessen the burden of AD for our patients.

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