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Emerging Systemic Treatment Options in Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic inflammatory condition that significantly affects the quality of life of both patients and their families or caregivers. Recently, treatment for moderate-to-severe AD were limited to conventional immunosuppressive therapies. However, currently, with the approval of biologic treatments and oral small molecules in the past decade, the effective and safe management of patients with AD is possible. Despite these advancements, challenges and unmet needs in clinical practice remain. This includes patients who do not respond well to or cannot tolerate existing treatment options and inadequate therapies that can modify the disease course. This review aimed to provide an overview of the current treatment approach for AD, highlight the current challenges in treatment, and discuss the rationale for novel treatment options and emerging evidence on systemic treatment options for AD.

Atopic dermatitis (AD) is a chronic and recurring inflammatory skin condition that significantly affects the quality of life of patients and their families/caregivers. It is characterized by impaired epidermal barrier function, Th2-mediated cutaneous inflammation, and skin dysbiosis, which are influenced by genetic and/or environmental factors.[1]

Recent advancements in understanding the pathogenesis of AD have generated groundbreaking changes in its therapeutic approaches.[2] In 2019, the Food and Drug Administration (FDA) approved the first biologic treatment for AD: dupilumab, an anti-interleukin-4/13 (anti-IL-4/13) monoclonal antibody. Following this milestone, oral Janus kinase (JAK) inhibitors, such as baricitinib, upadacitinib, and abrocitinib, and the anti-IL-13 monoclonal antibody tralokinumab were developed and approved.[3]

In comparison to one of the earliest treatment guidelines in 1992, which included limited systemic treatment options consisting of oral antihistamines, systemic corticosteroids, and conventional immunosuppressants such as cyclosporine, methotrexate, and azathioprine, as emerging therapies,[4] the latest EuroGuiDerm and USA guidelines recommend the utilization of biologic treatments, oral JAK inhibitors, and systemic immunosuppressive therapies. Most advancements in available treatment options, particularly for moderate-to-severe AD, emerged over the past decade.[3,5,6]

Although these options have resulted in more rapid and effective control of even extremely severe AD, it is crucial to note that AD is a highly heterogeneous disease, with patients exhibiting extensive responses to treatments. Additionally, the available treatments have limited efficacy and safety. Therefore, better delineation of atopic endophenotypes is required, which may pave the way for personalized medicine in AD. Novel treatment options to address these challenges are still needed.

This review provides a concise overview of the current treatment approach in AD and its limitations and investigates novel systemic treatment options and rationale behind their utilization in AD.

CURRENT TREATMENT APROACH IN ATOPIC DERMATITIS

The current diagnostic and treatment guidelines for AD recommend an approach based on disease severity determined using validated scoring systems such as the Eczema Area and Severity Index (EASI) or Scoring AD (SCORAD). These scoring systems evaluate various factors including the extent of AD lesions in different regions; degree of redness, thickness, lichenification, dryness, and swelling in the lesions; and intensity of scratching marks. In SCORAD, subjective symptoms such as itch and sleeplessness are further assessed. The score ranges for EASI and SCORAD are 0-72 and 0-103, respectively.[7,8] Based on these severity scores, patients can be categorized as having

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mild (EASI < 7; SCORAD < 25), moderate (EASI: 7-21; SCORAD: 25-50), or severe (EASI > 21; SCORAD > 50) AD.

The recommended baseline treatments for all patients include educational programs regarding the disease course, proper utilization of treatments, avoidance of triggering factors and allergens, and consistent and appropriate application of emollients to restore impaired skin barrier and address xerosis.[9]

For adult and pediatric patients with mild AD, treatment typically involves the use of topical corticosteroids and topical calcineurin inhibitors, and in cases of acute flare-ups, the application of topical corticosteroids with wet wraps is recommended. In moderately severe AD cases, a proactive approach involving the consistent use of topical corticosteroids and topical calcineurin inhibitors, combined with various phototherapy modalities such as narrowband ultraviolet B or medium-dose ultraviolet A1 and psychosomatic counseling, should be implemented.[6]

According to the latest treatment guidelines, advanced systemic treatments should be considered for severe AD. These may include medications such as dupilumab, baricitinib, abrocitinib, upadacitinib, and tralokinumab and conventional immunosuppressants including cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil, and systemic corticosteroids (Table 1). Notably, systemic corticosteroids are typically reserved for short-term rescue treatment because of their potential long-term side effects.[3,5,6]

CURRENT CLINICAL CHALLENGES IN SYSTEMIC TREATMENT OF ATOPIC DERMATITIS

Despite recent advancements in AD treatment, challenges and unmet needs persist in achieving safe and effective control of moderate-to-severe AD.

The primary challenge is unresponsiveness to advanced treatment options of a subset of patients. A recent meta-analysis of placebo-controlled clinical trials investigating targeted systemic therapies in AD revealed varying EASI-75 response rates. The response rates ranged between 39.7% and 62.7% for abrocitinib (100/200 mg), 17.9% and 29.5% for baricitinib (2/4 mg), 60.1% and 79.7% for upadacitinib (15/30 mg), and 44.2% and 51.3% for dupilumab (300 mg) when used as monotherapy.[10]

Real-life studies have demonstrated comparable efficacy to clinical trials. A systematic review of real-life studies on dupilumab showed EASI-50, EASI-75, and EASI-90 response rates of 85.1%, 59.8%, and 26.8%, respectively, among patients. These studies further indicated a mean EASI reduction of 69.6%.[11] In comparison to dupilumab, real-life evidence regarding the use of JAK inhibitors in AD is limited. However, a recent study indicated that treatment with upadacitinib resulted in an EASI-75 response in 76.7% of patients, similar to the response rates observed in clinical trials.[12] Additionally, abrocitinib treatment led to an EASI-75 response in 31.7% of the study population, which included patients who showed no response to biologics or JAK inhibitors.[13]

Overall, while the response rates observed in both clinical trials and real-life studies indicate significant improvement compared to the recent past, there remains patients who may benefit from alternative treatment options to achieve more effective disease control.

The second challenge is the adverse effects that restrict the utilization of recent advanced treatments, particularly in patients with comorbidities.

While largely derived from trials investigating rheumatic disorders, concerns regarding the increased risk of cardiovascular disease, cancer, serious infections, and thromboembolism associated with the use of tofacitinib[14] have led the European Medicines Agency (EMA) to recommend limiting the use of JAK inhibitors. This limitation applies to patients aged ≥ 65 years, those with an elevated cardiovascular or cancer risk, or those who smoke and should only be considered in those patient groups if a suitable alternative treatment is unavailable.

TABLE 1. Currently Approved/Recommended Systemic Treatment Options for Moderate-to-Severe AD.

Treatment	Recommended by the guidelines for[3,5]	Approved by the FDA for
Phototherapy (narrowband ultraviolet B/ ultraviolet A 1)	Children, adolescents, and adults	
Azathioprine	Children, adolescents, and adults	Off-license
Methotrexate	Children, adolescents, and adults	Off-license
Mycophenolate mofetil	Adults	Off-license
Cyclosporine A	Children, adolescents, and adults	Off-license (approved in Europe for ≥ 16 years)
Abrocitinib	Children, adolescents, and adults	≥ 12 years
Baricitinib	Adults	Off-license (approved in Europe for ≥ 18 years)
Upadacitinib	Children, adolescents, and adults	≥ 12 years
Dupilumab	Children, adolescents, and adults	≥ 6 months
Tralokinumab	Children, adolescents, and adults	≥ 12 years

AD, atopic dermatitis; FDA, the US Food and Drug Administration.

On the biologics side, the occurrence of dupilumab-induced conjunctivitis, observed in 26.1% of real-life study patients, may restrict its use.[11] Additionally, the reduced effectiveness of dupilumab in treating AD in the head and neck region poses another challenge in current clinical practice.[15]

Moreover, while cyclosporine has been recognized for AD treatment and has shown comparable effectiveness to dupilumab over a 16-week period in a systematic review and network meta-analysis, its long-term use has been restricted owing to side effects such as hypertension and renal toxicity.[16]

Finally, existing treatments do not exhibit a disease course-modifying effect, which is a long-term desirable outcome for novel treatments. With the enhanced understanding of the pathogenesis of AD, achieving this aim may be feasible in the future, underscoring the need for the exploration of novel targeted therapies.

EMERGING SYSTEMIC TREATMENTS FOR ATOPIC DERMATITIS

OX40-OX40L

The immune checkpoint molecule OX40 and its ligand OX40L belong to the tumor necrosis factor superfamily and its receptors. OX40 is expressed on both effector and regulatory T-cells and OX40L by various immune cells such as Langerhans, dendritic, and endothelial cells and macrophages. The interaction between OX40 and OX40L plays a critical role in the proliferation and survival of effector T-cells (i.e., Th1, Th2, Th17, and Th22) and the development of memory T-cells.[17] Previous studies have indicated an increase in OX40+ T-cells in the lesional skin of and elevated OX40 expression on circulating CD4+ T-cells in patients with AD. The OX40/OX40L interaction is implicated in the acute and chronic stages of AD by inducing T-cell differentiation, survival, cytokine production, and memory T-cell development.[18,19] Given the significance of the OX40/OX40L pathway in AD, the development of molecules inhibiting this pathway are underway: rocatinlimab (AMG451/KHK4083) and telazorlimab (GBR830) are anti-OX40 monoclonal antibodies, whereas amlitelimab (KY1005) targets OX40L.

A phase 1 clinical trial evaluated a regimen involving rocatinlimab infusions every 2 weeks for 6 weeks in 22 patients with AD. The most common adverse events were infusion-related fever (50%), chills (36.4%), aphthous ulcer (18.2%), and nasopharyngitis (13.6%). Despite these adverse events, a mean improvement of 24.2% in the EASI was noted at day 43. Interestingly, following a 16-week observation period without treatment, the mean improvement in EASI increased to 74.1%.[20] More recently, in a phase 2b trial, rocatinlimab (administered subcutaneously at doses of 150 mg every 4 weeks, 600 mg every 4 weeks, 300 mg every 2 weeks, and 600 mg every 2 weeks) was compared to placebo in 274 patients with AD over a 36-week treatment period, followed by a 20-week observation period without treatment. By week 16, the mean improvement in EASI was significantly better in the treatment group than in the placebo group (range; 48.3-61.1% vs. 15%). The EASI-75 response rate for the 300 mg every 2 weeks group was 53.8% at week 16; this response was sustained and even improved at weeks 24 (65.4%) and 36 (63.5%). A crucial observation from this study was the maintained significant difference even 20 weeks after the last treatment was administered. The most common reported adverse events were fever, chills, nasopharyngitis, headache, and aphthous ulcers.[21]

Telazorlimab was assessed in a phase 2a trial involving 62 patients with AD. After receiving two doses of telazorlimab on days 1 and 29, a notable EASI-50 response was observed in 76.9% of patients by day 71, compared to 37.5% of placebo patients. The treatment was well-tolerated, with headache being the most common adverse event, and its incidence was similar in both groups. Postprocedural infection and myalgia were frequently observed in the treatment group.[22] In the subsequent phase 2b trial, 313 and 149 patients were enrolled in two different parts (part 1: SC 300 mg Q2W vs. 300 mg Q4W vs. 75 mg Q4W vs. placebo; part 2: 600 mg Q2W vs. placebo). The study comprised a 38-week open-label period followed by a 12-week off-treatment follow-up after a 16-week placebo-controlled phase. At week 16, the mean EASI improvement was 54.4% vs. 34.2% for telazorlimab 300 mg Q2W vs. placebo in part 1, respectively. In part 2, EASI improvement at week 16 was 59% vs. 41.8% for telazorlimab 600 mg Q2W vs. placebo, respectively. The significant improvement observed during the placebo-controlled period was sustained throughout the open-label and off-treatment periods for up to 66 weeks. However, no significant difference was found in pruritus score between the treatment and placebo groups. Generally, treatment was well-tolerated, with the most common adverse events being nasopharyngitis, upper respiratory tract infections, and headache, with similar rates in the treatment and placebo groups.[23]

Amlitelimab targets OX40L, and the former two drugs inhibit OX40. A phase 1 trial demonstrated a tolerable safety profile in healthy participants, with headache being the most common adverse event.[24] Subsequently, a phase 2a trial evaluated the effectiveness and safety of amlitelimab in 89 patients with AD. Following a 16-week treatment period consisting of intravenous amlitelimab every 4 weeks, the mean improvement in EASI was 80.1%, 69.9%, and 49.3% in the high-dose (500 mg) amlitelimab, low-dose (200 mg) amlitelimab, and placebo groups, respectively. Moreover, the EASI-75 response at week 16 was higher in the treatment groups (59% vs. 52% vs. 25%). Response was observed as early as 2 weeks. Clinical improvements were maintained during the off-treatment follow-up period, even 24 weeks after the last dose administered. The occurrence rate of at least one treatment-emergent adverse events (TEAE) was 62%, 47%, and 69% in the low-dose, high-dose, and placebo groups, respectively. Headache, upper respiratory tract infections, fever, and increased aspartate aminotransferase were more frequent in the treatment groups.[25] Overall, the results from clinical trials of molecules targeting the OX40/OX40L pathway indicate that they could be safe and effective treatment options for AD. Furthermore, with the observed sustained treatment benefits during off-treatment periods, extending even weeks after the last treatment, the development of disease-modifying treatments is expected in the future.

Anti-IL-4/anti-IL-13

IL-4 and IL-13 play crucial roles in the pathogenesis of AD by promoting Th2 cell differentiation, keratinocyte apoptosis, and immunoglobulin E (IgE) production and impairing the skin barrier through reducing filaggrin, loricrin, and involucrin expressions.[26] Dupilumab, which inhibits IL-4 and IL-13 by targeting IL-4Rα, the subunit of types I and II IL-4 receptors, has shown promising results. Similarly, tralokinumab and lebrikizumab, monoclonal antibodies targeting IL-13 and related pathways, have demonstrated favorable results in clinical trials[27] and received approval for use in patients aged ≥12 with AD by the FDA and EMA, respectively.[28]

In a phase 2 trial, lebrikizumab, a monoclonal antibody targeting the soluble IL-13 binding site of the IL-4Rα, showed superiority over placebo, with 82.4% of patients achieving an EASI-50 response at week 12 compared to 62.3% in the placebo group. Conjunctivitis incidence was 9.6% and 7.5% in the treatment and placebo groups, respectively.[29] In another phase 2 study involving 280 patients, the mean improvement in EASI score was -62.3-72.1% for the treatment group compared to -41.1% for the placebo group.[30]

Tralokinumab, which also targets IL-13 but binds to IL-13Rα1 and IL-13Rα2 sites, exhibited promising results in a phase 2 trial. Treatment with tralokinumab led to an Investigator Global Assessment (IGA) 0/1 response in 27% of patients and an EASI-50 response in 73%, both significantly higher than the placebo arm.[31] Moreover, in three phase 3 trials, tralokinumab showed significant improvement in IGA and EASI scores and positive effects on itch and sleep.[32]

Lebrikizumab and tralokinumab demonstrated lower rates of conjunctivitis compared to dupilumab. The rate of conjunctivitis was significantly lower with lebrikizumab compared to tralokinumab,[33] which could be advantageous in clinical practice. However, further confirmation through real-life studies is warranted.

Following the success achieved with the inhibition of the IL-4/IL-13 pathway, numerous novel antibodies targeting this pathway are currently in development.

Rademikibart (CPB-201) is another IgG4 kappa monoclonal antibody targeting IL-4Rα.

Preclinical studies indicated that rademikibart exhibits a higher affinity for IL-4Rα compared to dupilumab.[34] The results of two phase 1 clinical trials on rademikibart have demonstrated a favorable safety profile. In these trials, rademikibart was administered at 75 mg, 150 mg, 300 mg, and 600 mg compared to placebo, both as single doses and in four weekly doses (phase 1b). The incidence of TEAEs was low and mostly mild, comparable to that in the placebo group. The most frequent TEAEs were headache and upper respiratory tract infection. In the phase 1b trial evaluating the effects of rademikibart after a 4-week treatment, results from different doses showed a significant improvement in various outcome measures compared to baseline and placebo. Specifically, a substantial reduction was noted in EASI score by 68.4%, body surface area involvement by 53.9%, Dermatology Life Quality Index by 68%, and Pruritus Numerical Rating Scale by 46.7%. These indicate that rademikibart is a favorable treatment option for AD.[35]

Recently, the results of a phase 2 placebo-controlled trial investigating the efficacy of rademikibart in adult patients with moderate-to-severe AD were published. The trial included 226 participants who received a loading dose of 600 mg followed by rademikibart subcutaneous injections at 300 mg every 2 weeks (Q2W), 150 mg every 2 weeks (Q2W), and 300 mg every 4 weeks (Q4W) or placebo for 16 weeks. At week 16, the mean reduction in EASI score was 63% in the 300 mg Q2W group, 58% in the 150 mg Q2W group, 63% in the 300 mg Q4W group, and 39% in the placebo group. The rates of TEAEs, such as herpes and conjunctivitis, were similar between the treatment and placebo groups. These findings show that rademikibart may be effective in reducing disease severity in patients with moderate-to-severe AD, with a safety profile comparable to placebo.[36]

Another humanized monoclonal antibody targeting IL-4Rα is CM310, also called stapokibart. In a phase 2b trial, 120 adult patients were randomized into groups receiving 300 mg, 150 mg, or placebo every 2 weeks for 16 weeks. At week 16, the percentage of EASI-75 responders was 70%, 65%, and 20% in the high-dose CM310, low-dose CM310, and placebo groups, respectively. The rate of TEAEs was similar between the groups, with upper respiratory tract infection, hyperlipidemia, and hyperuricemia being the most common.[37]

Another therapeutic approach in targeting IL-4/IL-13 pathway is blocking IL-13Rα, which is a component of type II IL-4R that mediates IL-4 and IL-13 signals through JAK1-TYK2 and STAT3-STAT6.

Eblasakimab, a monoclonal antibody targeting IL-13Rα1, was evaluated in a phase 1b study involving 52 patients with moderate-to-severe AD. Participants received subcutaneous eblasakimab at 200 mg, 400 mg, and 600 mg or placebo weekly for 8 weeks. The rates of TEAEs in the placebo and eblasakimab groups were 47% and 71%, respectively, with none leading to study discontinuation. Furthermore, the mean change in EASI score at week 8 was significantly higher in the treatment group than in the placebo group (-65% vs. -27%).[38] Considering the potential for increased efficacy with longer treatment duration and low prevalence of conjunctivitis (6%) compared to therapies targeting type I IL-4R, eblasakimab appears to be a promising option in AD treatment.

Anti-IL-31

IL-31 plays a critical role in AD-related pruritus, along with its pro-inflammatory and immunomodulatory functions. Inhibiting IL-31 through its receptor, IL-31RA, is a promising treatment approach for AD.[39] Nemolizumab, an anti-IL-31RA monoclonal antibody, has demonstrated significant reduction in pruritus in both phase 2b and phase 3 placebo-controlled trials following 16-24 weeks of treatment.[40,41]

Two recent long-term phase 3 trials of nemolizumab 60 mg administered every 4 weeks, combined with topical corticosteroids/calcineurin inhibitors, demonstrated a significant and sustained decrease in pruritus over 68 weeks. The reduction from baseline pruritus visual analog scale scores at week 68 reached 65.9%, and a notable improvement of 78% in EASI scores compared to baseline was found. Remarkably, these improvements were maintained

during the 12-week follow-up without treatment. Additionally, most adverse effects were mild, with the most common severe TEAEs being nasopharyngitis (33.9%) and AD exacerbation (25.2%).[42]

In a recent phase 3 trial involving children aged 6-12 years with AD experiencing uncontrolled pruritus despite topical treatments and oral antihistamines, significant improvement in pruritus was observed with nemolizumab compared to placebo. Notably, the benefits of nemolizumab were evident as early as day 2, and improvement in quality of life was observed. However, notably, the improvement in EASI response rates between the two groups was not statistically significant.[43]

Despite its relatively limited effect on skin lesions, nemolizumab may be a viable option for patients with AD in whom pruritus cannot be adequately controlled with existing treatments. In 2022, the use of nemolizumab was approved for AD-related itch in adults and children aged > 12 years in Japan.

Anti-IL-36

IL-36 is a pro-inflammatory cytokine known for its involvement in antigen presentation and immune activation.[44] While its role in pustular psoriasis (generalized and palmoplantar) is well-established, evidenced by the approval of spesolimab, an anti-IL-36R monoclonal antibody, for use in generalized pustular psoriasis in adults, accumulating evidence indicating its involvement in AD has been noted. This includes its role in *Staphylococcus aureus*-mediated skin inflammation.[45,46]

In a phase 2a clinical trial involving 71 adults with AD, the mean change in EASI score at 16 weeks did not show a significant difference between spesolimab and placebo. However, in another analysis excluding patients who received systemic/topical corticosteroids within the study period, a significant difference between the two groups was observed. Furthermore, the treatment was well-tolerated. Despite this, the results of the trial show a limited role for IL-36 inhibition in AD.[47]

Anti-CCR4

Induction of Th2 cells to the inflammation site is a prerequisite for the development and maintenance of type 2 inflammation. This is mediated by two major ligands of the C-C motif chemokine receptor 4 (CCR4): C-C motif chemokine ligand 17 (CCL17) and CCL22.[48] In mouse models, CCR4 has been demonstrated to play a crucial role in the induction of Th2 cells to the skin following antigen exposure.[49]

CCR4 antagonists may play a role in inhibiting type 2 inflammation in AD. RPT193, an oral small molecule targeting CCR4, is currently under investigation for use in AD and asthma. In a phase 1a/1b placebo-controlled study of RPT193 (administered at 400 mg or placebo once daily for 28 days), an EASI-50 response at day 29 was observed in 42.9% of the treatment group compared to 10% in the placebo group. The difference between the two groups became even more pronounced at day 43, following a 2-week off-treatment follow-up period. This sustained clinical effect following treatment cessation may be related to reduced accumulation of Th2 cells in the tissue and decreased production of pro-inflammatory cytokines. The treatment with RPT193 was generally well-tolerated, with only mild-to-moderate adverse events reported, with nausea being the most frequent.[50]

Anti-IRAK4

IL-1 receptor-associated kinase 4 (IRAK4) has regulatory functions in innate immunity and is involved in signaling pathways of Toll-like receptors and interleukin-1 receptors (IL-1Rs).[51] Hence, IRAK4 inhibitors may exert an inhibitory effect on all IL-1 cytokines, making them a potential treatment alternative for rheumatoid arthritis, hidradenitis suppurativa, and AD.[52]

KT-474 (SAR444656) is an oral small-molecule degrader of IRAK4. A recent clinical proof-of-concept study with KT-474 included seven patients with AD. Following a 28-day treatment, the mean improvement in EASI and pruritus scores were 37.1% and 51.3%, respectively, with a tolerable safety profile. These improvements were sustained during the 2-week post-treatment follow-up period. The results of this study indicate that inhibition of IRAK4 may be an effective and safe option in AD. Clinical trials with longer treatment periods may demonstrate higher efficacy.[53]

Substance P antagonists

Substance P (SP) emerges as a pivotal mediator of pruritus, the hallmark symptom of AD. Previous studies have demonstrated alterations in SP levels and its positivity in nerve fibers between lesional and healthy skin of AD patients.[54] Additionally, elevated serum SP levels in AD have been documented.[55] Besides its involvement in pruritus, SP exhibits pro-inflammatory effects. Animal studies have demonstrated that inhibiting neurokinin 1, the main receptor of SP, effectively suppresses scratching behavior.[56]

Considering this evidence, an earlier study investigated the efficacy of aprepitant, an NK-1 antagonist, in combination with standardized topical treatment in 19 adult patients with AD, compared to a control group receiving only topical treatment. However, no significant difference was observed between the aprepitant and topical-only groups. Possible reasons for this ineffectiveness may include the relatively low dose of aprepitant and short treatment duration.[57]

More recently, a phase 3 randomized, placebo-controlled trial enrolled 375 patients with AD who received tradipitant treatment, another NK-1 antagonist. Although there was a numerical difference in the reduction of pruritus compared to placebo, this benefit did not reach statistical significance. However, when only patients with mild lesion severity (IGA 1 or 2) were included in the analysis, the reduction in pruritus and improvement in sleep time were significantly higher in the treatment group. This indicates a potential role for NK-1 antagonist in patients with mild lesion severity but high levels of pruritus.[58]

Other treatments

Dysregulation of the opioid system is considered a factor contributing to the development of pruritus in AD. Therefore, considering the inhibitory effects of kappa-opioid receptor (KOR) agonists on uremic pruritus and observed downregulation of KOR in AD, a phase 2 trial investigating the effect of oral difelikefalin in AD with severe pruritus was conducted.[59-61] In this trial, at week 12, the difference in pruritus

scores was numerical and failed to reach statistical significance. However, when analyzing patients with mild-to-moderate lesion severity and moderate-to-severe itch (itch-dominant type), pruritus reduction was significantly higher in the treatment group at week 12. Treatment was generally well-tolerated, with abdominal pain/discomfort, nausea, dry mouth, headache, hypertension, and dizziness being the most frequent TEAEs. Additionally, a change in cutaneous inflammatory markers and increased skin barrier gene expression have been demonstrated.[61] Whether these effects are directly related to difelikefalin or an indirect result of breaking the itch-scratch cycle remains unclear. Overall, these results warrant further investigation into the role of difelikefalin in AD, particularly in patients with severe pruritus. Another potential therapeutic target in AD is IL-33, an alarmin produced by epithelial cells and released during cell injury.[62] Its receptor ST2 is expressed on keratinocytes and various inflammatory cells such as T-lymphocytes, basophils, and eosinophils. The IL-33/ST2 pathway is implicated in the induction of type 2 inflammation and reduction of filaggrin expression, which can be significant in AD development.[63,64] Etokimab, an anti-IL-33 monoclonal antibody, showed promising results in 12 adult patients with AD in a phase 2a proof-of-concept study. Following a single intravenous dose of etokimab at 300 mg, 83.3% of the patients

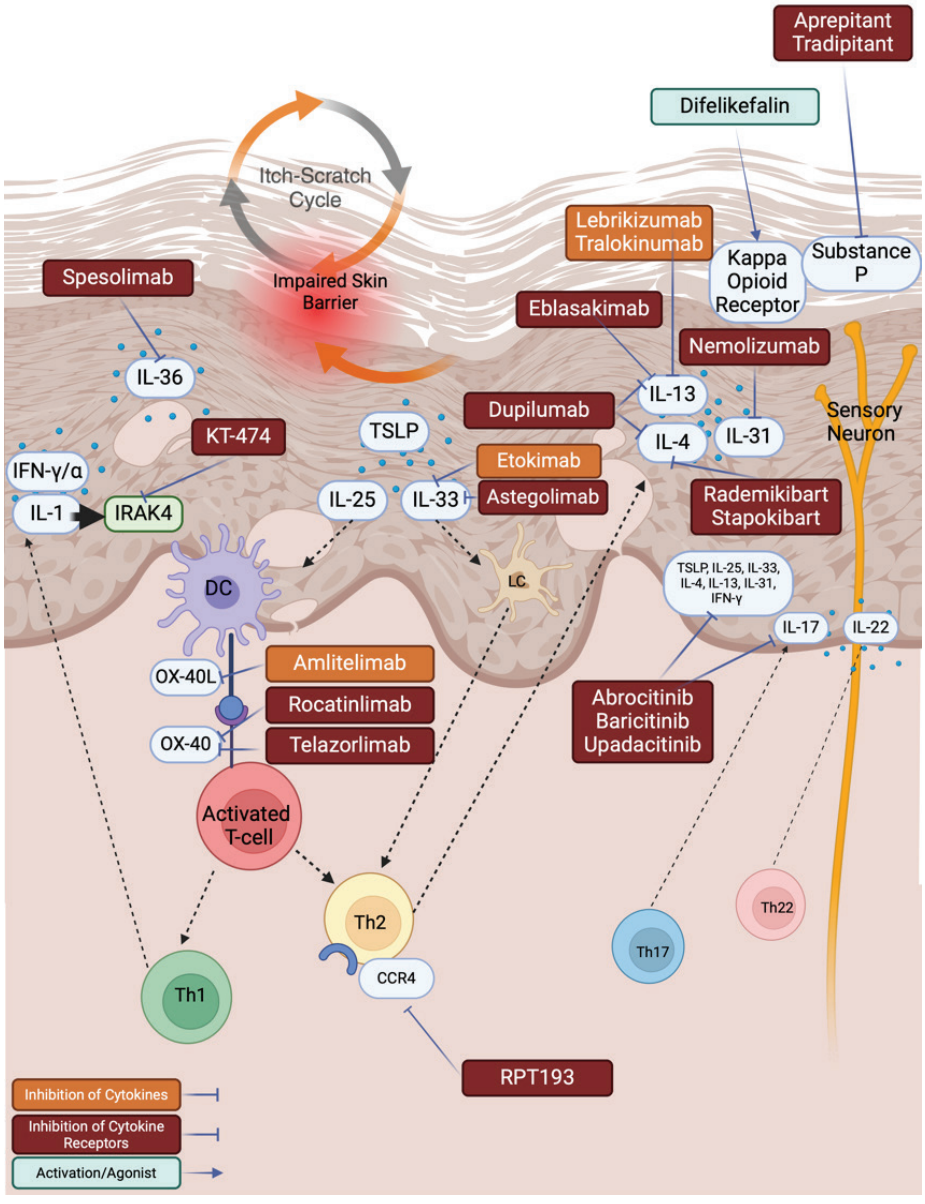

FIG. 1. Target molecules in the pathogenesis of atopic dermatitis and advanced/emerging systemic treatments.
DC, dendritic cells; IL, interleukin; IRAK4, IL-1 receptor-associated kinase 4; LH, Langerhans cells; TSLP, thymic stromal lymphopoietin; IFN-γ; interferon gamma (created with BioRender.com).

TABLE 2. Ongoing Clinical Trials of Systemic Treatments in AD (clinicaltrials.gov).

Treatment	Route	Target	Study population	Clinical phase	NCT number
Rezpegaldesleukin (Rezpeg)	SC	IL-2	> 18 years	Phase 2b	NCT06136741
BMS-986326	IV/SC	IL-2-CD25	> 18 years	Phase 1	NCT06248814
MG-K10	SC	IL-4Rα	> 18 years	Phase 3	NCT06026891
Stapokibart (CM310)	SC	IL-4Rα	> 18 years	Phase 2	NCT06116565
	SC	IL-4Rα	> 18 years	Phase 2	NCT05715320
TQH2722	SC	IL-4Rα	> 18 years	Phase 3	NCT05970432
PF-07275315	IV/SC	IL-4/IL-13/TSLP	> 18 years	Phase 2	NCT05995964
NM26-2198	SC	IL-4Rα + IL-31 Bispecific MAb	> 18 years	Phase 1	NCT05859724
AK120	SC	IL-4Rα	> 18 years	Phase 2	NCT05048056
	SC	IL-4Rα	> 18 years	Phase 3	NCT06383468
GR1802	SC	IL-4Rα	> 18 years	Phase 3	NCT06216392
Bempikibart (ADX-914)	SC	IL-7Rα	> 18 years	Phase 2	NCT05509023
APG777	SC	IL-13	> 18 years	Phase 2	NCT06395948
LEO 138559	SC	IL-22RA1	> 18 years	Phase 2	NCT05923099
CM326	SC	TSLP	> 18 years	Phase 2	NCT05671445
TAVO101	IV	TSLP	> 18 years	Phase 2	NCT06176040
GR2002	SC	TSLP	> 18 years	Phase 1	NCT06175143
Rocatinlimab	SC	OX40	> 18 years	Phase 3	NCT05398445
	SC	OX40	≥ 12 - < 18 years	Phase 3	NCT05704738
	SC	OX40	≥ 12 years	Phase 3	NCT05882877
Amlitelimab	SC	OX40L	≥ 12 years	Phase 2	NCT05769777
	SC	OX40L	≥ 12 years	Phase 2	NCT06130566
RBN-3143	Oral	PARP14	> 18 years	Phase 1	NCT05215808
QY201	Oral	JAK1/TYK2	> 18 years	Phase 1b/2	NCT05525715
LNK01001	Oral	JAK1	> 18 years	Phase 3	NCT06277245
EP262	Oral	MRGPRX2	> 18 years	Phase 2a	NCT06144424
KT-474 (SAR444656)	Oral	IRAK4	> 18 years	Phase 2	NCT06058156
OpSCF	SC	Stem cell factor	> 18 years	Phase 2	NCT06101823
FB825	SC	Membrane-bound IgE (mIgE)	> 18 years	Phase 2	NCT06397911

AD, atopic dermatitis; IL: interleukin; JAK, Janus kinase; TSLP, thymic stromal lymphopoietin; IRAK4: IL-1 receptor-associated kinase 4; IgE, immunoglobulin E.

showed an EASI-50 response at day 29 with only mild and transient adverse events.[65] However, etokimab failed to demonstrate a superior EASI-50 response rate over placebo in a subsequent phase 2b study. Similarly, astegolimab, an anti-IL-33R (ST2) monoclonal antibody, failed to provide a better EASI improvement compared to placebo in a 16-week phase 2 trial (treatment vs. placebo: -51.4% vs. -58.2%). These results show that sole inhibition of the IL-33/ST2 pathway may be insufficient to provide significant clinical benefit in AD.[66] In conclusion, in line with recent advancements in understanding the pathogenesis of AD, there is a growing array of molecules targeting crucial pathways in the condition (Figure 1, Table 2). Specifically, those focusing on OX40/OX40L and IL4/IL13 pathways are promising prospects for effectively and safely managing AD. This raises hopes for achieving the aim of disease modification in the future, potentially ushering in an era of precision medicine for AD.

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REFERENCES

1. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers.* 2018;4:1. [CrossRef]
2. Trier AM, Kim BS. Insights into atopic dermatitis pathogenesis lead to newly approved systemic therapies. *Br J Dermatol.* 2023;188:698-708. [CrossRef]
3. Davis DMR, Drucker AM, Alikhan A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. *J Am Acad Dermatol.* 2024;90:e43-e56. [CrossRef]
4. Guidelines of care for atopic dermatitis. *J Am Acad Dermatol.* 1992;26:485-488. [CrossRef]
5. Wollenberg A, Kinberger M, Arents B, et al. First update of the living European guideline (EuroGuiDerm) on atopic eczema. *J Eur Acad Dermatol Venereol.* 2023;37:e1283-1287. [CrossRef]
6. Wollenberg A, Kinberger M, Arents B, et al. European guideline (EuroGuiDerm) on atopic eczema: part I - systemic therapy. *J Eur Acad Dermatol Venereol.* 2022;36:1409-1431. [CrossRef]
7. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical Validation and Guidelines for the SCORAD Index: Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology.* 1997;195:10-19. [CrossRef]
8. Tofte S, Graeber M, Cherill R, Omoto M, Thurston M, Hanifin J. Eczema area and severity index (EASI): A new tool to evaluate atopic dermatitis. *J Eur Acad Dermatol Venereol.* 1998;11:S197. [CrossRef]
9. Wollenberg A, Kinberger M, Arents B, et al. European guideline (EuroGuiDerm) on atopic eczema - part II: non-systemic treatments and treatment recommendations for special AE patient populations. *J Eur Acad Dermatol Venereol.* 2022;36:1904-1926. [CrossRef]
10. Silverberg JI, Hong HC, Calimlim BM, et al. Comparative Efficacy of Targeted Systemic Therapies for Moderate-to-Severe Atopic Dermatitis without Topical Corticosteroids: An Updated Network Meta-analysis. *Dermatol Ther (Heidelb).* 2023;13:2247-2264. [CrossRef]
11. Halling AS, Loft N, Silverberg JI, Guttman-Yassky E, Thyssen JP. Real-world evidence of dupilumab efficacy and risk of adverse events: A systematic review and meta-analysis. *J Am Acad Dermatol.* 2021;84:139-147. [CrossRef]
12. Pereyra-Rodriguez JJ, Herranz P, Figueras-Nart I, et al. Treatment of Severe Atopic Dermatitis With Upadacitinib in Clinical Practice: Short-Term Efficacy and Safety Results. *J Invest Allergol Clin Immunol.* 2023;33:211-213. [CrossRef]
13. Olydam JI, Schlösser AR, Custurone P, Nijsten TEC, Hijnen D. Real-world effectiveness of abrocitinib treatment in patients with difficult-to-treat atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2023;37:2537-2542. [CrossRef]
14. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N Engl J Med.* 2022;386:316-326. [CrossRef]
15. Vittrup I, Krogh NS, Larsen HHP, et al. A nationwide 104 weeks real-world study of dupilumab in adults with atopic dermatitis: Ineffectiveness in head-and-neck dermatitis. *J Eur Acad Dermatol Venereol.* 2023;37:1046-1055. [CrossRef]
16. Drucker AM, Morra DE, Prieto-Merino D, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. *JAMA Dermatol.* 2022;158:523-532. [CrossRef]
17. Croft M, Esfandiari E, Chong C, et al. OX40 in the Pathogenesis of Atopic Dermatitis-A New Therapeutic Target. *Am J Clin Dermatol.* 2024;25:447-461. [CrossRef]
18. Furue M, Furue M. OX40L-OX40 Signaling in Atopic Dermatitis. *J Clin Med.* 2021;10:2578. [CrossRef]
19. Elsner JS, Carlsson M, Stougaard JK, et al. The OX40 Axis is Associated with Both Systemic and Local Involvement in Atopic Dermatitis. *Acta Derm Venereol.* 2020;100:adv00099. [CrossRef]
20. Lé AM, Torres T. OX40-OX40L Inhibition for the Treatment of Atopic Dermatitis-Focus on Rocatinlimab and Amlitelimab. *Pharmaceutics.* 2022;14:2753. [CrossRef]
21. Guttman-Yassky E, Simpson EL, Reich K, et al. An anti-OX40 antibody to treat moderate-to-severe atopic dermatitis: a multicentre, double-blind, placebo-controlled phase 2b study. *Lancet.* 2023;401:204-214. [CrossRef]
22. Guttman-Yassky E, Pavel AB, Zhou L, et al. GBR 830, an anti-OX40, improves skin gene signatures and clinical scores in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2019;144:482-493.e7. [CrossRef]
23. Rewerska B, Sher LD, Alpizar S, et al. Phase 2b randomized trial of OX40 inhibitor telazorlimab for moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol Glob.* 2024;3:100195. [CrossRef]
24. Saghari M, Gal P, Gilbert S, et al. OX40L Inhibition Suppresses KLH-driven Immune Responses in Healthy Volunteers: A Randomized Controlled Trial Demonstrating Proof-of-Pharmacology for KY1005. *Clin Pharmacol Ther.* 2022;111:1121-1132. [CrossRef]
25. Weidinger S, Bieber T, Cork MJ, et al. Safety and efficacy of amlitelimab, a fully human nondepleting, noncytotoxic anti-OX40 ligand monoclonal antibody, in atopic dermatitis: results of a phase IIa randomized placebo-controlled trial. *Br J Dermatol.* 2023;189:531-539. [CrossRef]
26. Huang IH, Chung WH, Wu PC, Chen CB. JAK-STAT signaling pathway in the pathogenesis of atopic dermatitis: An updated review. *Front Immunol.* 2022;13:1068260. [CrossRef]
27. Bieber T. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. *Allergy.* 2020;75:54-62. [CrossRef]
28. Zhang Y, Jing D, Cheng J, Chen X, Shen M, Liu H. The efficacy and safety of IL-13 inhibitors in atopic dermatitis: A systematic review and meta-analysis. *Front Immunol.* 2022;13:923362. [CrossRef]
29. Simpson EL, Flohr C, Eichenfield LF, et al. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE). *J Am Acad Dermatol.* 2018;78:863-871.e11. [CrossRef]
30. Guttman-Yassky E, Blauvelt A, Eichenfield LF, et al. Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial. *JAMA Dermatol.* 2020;156:411-420. [CrossRef]
31. Wollenberg A, Howell MD, Guttman-Yassky E, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol.* 2019;143:135-141. [CrossRef]
32. Simpson EL, Guttman-Yassky E, Eichenfield LF, et al. Tralokinumab therapy for moderate-to-severe atopic dermatitis: Clinical outcomes with targeted IL-13 inhibition. *Allergy.* 2023;78:2875-2891. [CrossRef]
33. Labib A, Ju T, Yosipovitch G. Managing Atopic Dermatitis with Lebrikizumab - The Evidence to Date. *Clin Cosmet Investig Dermatol.* 2022;15:1065-1072. [CrossRef]
34. Zhang L, Ding Y, Wang Q, et al. Preclinical immunological characterization of rademikibart (CBP-201), a next-generation human monoclonal antibody targeting IL-4Rα, for the treatment of Th2 inflammatory diseases. *Sci Rep.* 2023;13:12411. [CrossRef]
35. Wang J, White J, Sansone KJ, et al. Rademikibart (CBP-201), a next-generation monoclonal antibody targeting human IL-4Rα: Two phase I randomized trials, in healthy individuals and patients with atopic dermatitis. *Clin Transl Sci.* 2023;16:2614-2627. [CrossRef]
36. Silverberg JI, Strober B, Feinstein B, et al. Efficacy and safety of rademikibart (CBP-201), a next-generation mAb targeting IL-4Rα, in adults with moderate to severe atopic dermatitis: A phase 2 randomized trial (CBP-201-WW001). *J Allergy Clin Immunol.* 2024;153:1040-1049.e12. [CrossRef]
37. Zhao Y, Zhang J, Yang B, et al. Efficacy and safety of CM310 in moderate-to-severe atopic dermatitis: A multicenter, randomized, double-blind, placebo-controlled phase 2b trial. *Chin Med J (Engl).* 2024;137:200-208. [CrossRef]
38. Veverka KA, Thng STG, Silverberg JI, et al. Safety and efficacy of eblasakimab, an interleukin 13 receptor α1 monoclonal antibody, in adults with moderate-to-severe atopic dermatitis: A phase 1b, multiple-ascending dose study. *J Am Acad Dermatol.* 2024;90:504-511. [CrossRef]
39. Furue M, Yamamura K, Kido-Nakahara M, Nakahara T, Fukui Y. Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis. *Allergy.* 2018;73:29-36. [CrossRef]
40. Silverberg JI, Pinter A, Pulka G, et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *J Allergy Clin Immunol.* 2020;145:173-182. [CrossRef]
41. Kabashima K, Matsumura T, Komazaki H, Kawashima M; Nemolizumab-JP01 Study Group. Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus. *N Engl J Med.* 2020;383:141-150. [CrossRef]
42. Kabashima K, Matsumura T, Komazaki H, Kawashima M; Nemolizumab JP01 andJP02 Study Group. Nemolizumab plus topical agents in patients with atopic dermatitis (AD) and moderate-to-severe pruritus provide improvement in pruritus and signs of AD for up to 68 weeks: results from two phase III, long-term studies. *Br J Dermatol.* 2022;186:642-651. [CrossRef]
43. Igarashi A, Katsunuma T, Matsumura T, Komazaki H; Nemolizumab-JP04 Study Group. Efficacy and safety of nemolizumab in paediatric patients aged 6-12 years with atopic dermatitis with moderate-to-severe pruritus: results from a phase III, randomized, double-blind, placebo-controlled, multicentre study. *Br J Dermatol.* 2024;190:20-28. [CrossRef]

44. Yuan ZC, Xu WD, Liu XY, Liu XY, Huang AF, Su LC. Biology of IL-36 Signaling and Its Role in Systemic Inflammatory Diseases. *Front Immunol.* 2019;10:2532. [CrossRef]
45. Otobe S, Sugaya M, Nakajima R, et al. Increased interleukin-36γ expression in skin and sera of patients with atopic dermatitis and mycosis fungoides/Sézary syndrome. *J Dermatol.* 2018;45:468-471. [CrossRef]
46. Liu H, Archer NK, Dillen CA, et al. Staphylococcus aureus Epicutaneous Exposure Drives Skin Inflammation via IL-36-Mediated T Cell Responses. *Cell Host Microbe.* 2017;22:653-666.e5. [CrossRef]
47. Bissonnette R, Abramovits W, Saint-Cyr Proulx É, et al. Spesolimab, an anti-interleukin-36 receptor antibody, in patients with moderate-to-severe atopic dermatitis: Results from a multicentre, randomized, double-blind, placebo-controlled, phase IIa study. *J Eur Acad Dermatol Venereol.* 2023;37:549-557. [CrossRef]
48. Horikawa T, Nakayama T, Hikita I, et al. IFN-gamma-inducible expression of thymus and activation-regulated chemokine/CCL17 and macrophage-derived chemokine/CCL22 in epidermal keratinocytes and their roles in atopic dermatitis. *Int Immunol.* 2002;14:767-773. [CrossRef]
49. Oyoshi MK, Elkhal A, Scott JE, et al. Epicutaneous challenge of orally immunized mice redirects antigen-specific gut-homing T cells to the skin. *J Clin Invest.* 2011;121:2210-2220. [CrossRef]
50. Bissonnette R, DuBois J, Facheris P, et al. Clinical and molecular effects of oral CCR4 antagonist RPT193 in atopic dermatitis: A Phase 1 study. *Allergy.* 2024;79:924-936. [CrossRef]
51. Pereira M, Gazzinelli RT. Regulation of innate immune signaling by IRAK proteins. *Front Immunol.* 2023;14:1133354. [CrossRef]
52. Lavazais S, Jargosch M, Dupont S, et al. IRAK4 inhibition dampens pathogenic processes driving inflammatory skin diseases. *Sci Transl Med.* 2023;15:eabj3289. [CrossRef]
53. Ackerman L, Acloque G, Bacchelli S, et al. IRAK4 degrader in hidradenitis suppurativa and atopic dermatitis: a phase 1 trial. *Nat Med.* 2023;29:3127-3136. [CrossRef]
54. Salomon J, Baran E. The role of selected neuropeptides in pathogenesis of atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2008;22:223-228. [CrossRef]
55. Teresiak-Mikołajczak E, Czarnecka-Operacz M, Jenerowicz D, Silny W. Neurogenic markers of the inflammatory process in atopic dermatitis: relation to the severity and pruritus. *Postepy Dermatol Alergol.* 2013;30:286-292. [CrossRef]
56. Ohmura T, Hayashi T, Satoh Y, Konomi A, Jung B, Satoh H. Involvement of substance P in scratching behaviour in an atopic dermatitis model. *Eur J Pharmacol.* 2004;491:191-194. [CrossRef]
57. Lönndahl L, Holst M, Bradley M, et al. Substance P antagonist aprepitant shows no additive effect compared with standardized topical treatment alone in patients with atopic dermatitis. *Acta Derm Venereol.* 2018;98:324-328. [CrossRef]
58. Welsh SE, Xiao C, Kaden AR, et al. Neurokinin-1 receptor antagonist tradipitant has mixed effects on itch in atopic dermatitis: results from EPIONE, a randomized clinical trial. *J Eur Acad Dermatol Venereol.* 2021;35:e338-e340. [CrossRef]
59. Erickson S, Heul AV, Kim BS. New and emerging treatments for inflammatory itch. *Ann Allergy Asthma Immunol.* 2021;126:13-20. [CrossRef]
60. Tominaga M, Ogawa H, Takamori K. Possible roles of epidermal opioid systems in pruritus of atopic dermatitis. *J Invest Dermatol.* 2007;127:2228-2235. [CrossRef]
61. Guttman-Yassky E, Facheris P, Da Rosa JC, et al. Oral difelikefalin reduces moderate to severe pruritus and expression of pruritic and inflammatory biomarkers in subjects with atopic dermatitis. *J Allergy Clin Immunol.* 2023;152:916-926. [CrossRef]
62. Savinko T, Matikainen S, Saarialho-Kere U, et al. IL-33 and ST2 in atopic dermatitis: expression profiles and modulation by triggering factors. *J Invest Dermatol.* 2012;132:1392-1400. [CrossRef]
63. Ding W, Zou GL, Zhang W, Lai XN, Chen HW, Xiong LX. Interleukin-33: Its Emerging Role in Allergic Diseases. *Molecules.* 2018;23:1665. [CrossRef]
64. Nygaard U, van den Bogaard EH, Niehues H, et al. The "Alarmins" HMBG1 and IL-33 Downregulate Structural Skin Barrier Proteins and Impair Epidermal Growth. *Acta Derm Venereol.* 2017;97:305-312. [CrossRef]
65. Chen YL, Gutowska-Owsiak D, Hardman CS, et al. Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. *Sci Transl Med.* 2019;23:eaax2945. [CrossRef]
66. Maurer M, Cheung DS, Theess W, et al. Phase 2 randomized clinical trial of astegolimab in patients with moderate to severe atopic dermatitis. *J Allergy Clin Immunol.* 2022;150:1517-1524. [CrossRef]