Emerging Systemic Therapeutic Biologics and Small Molecules for Atopic Dermatitis: How to Decide Which Treatment Is Right for Your Patients

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Learning objectives:

1. To evaluate clinical characteristics and severity of atopic dermatitis (AD) and distinguish it from other diseases.

2. To describe the underlying cellular and molecular mechanisms contributing to AD pathogenesis.

3. To describe current and emerging systemic therapeutics for AD.

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Abbreviations used
ACD- Allergic contact dermatitis
AD- Atopic dermatitis
AE- Adverse effect
cAMP- Cyclic adenosine monophosphate
CI- Confidence interval
CsA- Cyclosporine
DC- Dendritic cell
EASI- Eczema Area and Severity Index
H4R- H4 receptor
HOME- Harmonizing Outcome Measurement for Eczema
IGA- Investigator's Global Assessment
JAK- Janus kinase
mAb- Monoclonal antibody
NRS- Numeric rating scale
OSMR- Oncostatin M receptor
PDE-4- Phosphodiesterase enzyme 4
SCORAD- SCORing Atopic Dermatitis
STAT- Signal transducer and activator of transcription
SYK- Spleen tyrosine kinase
TCS- Topical corticosteroid
Th- T helper
TRPA1- Transient receptor channel potential cation channel ankyrin subtype 1
TRPV1- Transient receptor potential cation channel vanilloid subtype 1
TSLP- Thymic stromal lymphopoietin

The evolving discoveries in atopic dermatitis (AD) broaden our understanding of the pathogenesis of the disease and, above all, enable better management for patients. Dupilumab was the first biologic for AD, and since its approval, many new treatments have emerged in both late- and early-stage clinical trials. These trials have led to a further understanding of the pathogenesis of AD and to the identification of additional potential therapeutic targets. This review will highlight the emerging therapies and provide approaches on how to choose the right treatment for your patients. **(J Allergy Clin Immunol Pract 2021;9:1449-60)**

Key words: *Atopic dermatitis; Targeted agent; New systemic treatments; Treatment options*

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease, with pruritus as the main symptom. Recent prevalence estimates of childhood AD in the United States range from 6% to 12.98%.[1,2] Recent studies of 27,157 and 34,613 adults (aged 18-85 years) from the 2010 National Health Interview Survey and 2012 National Health Interview Survey found a 1-year prevalence of AD in adults to be 10.2% and 7.2%, respectively.[3] AD prevalence has increased worldwide over the past 50 years. Although the cause of the increase is unknown, several systematic large-scale studies point to numerous genetic and environmental factors as potential causes.[4] As our understanding of the disease pathogenesis improves, novel systemic agents emerge, particularly to address the therapeutic gap for patients with moderate-to-severe disease not adequately controlled with topical therapy. Patients with moderate-to-severe disease represent approximately 25% of the AD population.[2] Exactly how many patients require systemic therapy is unclear but is likely substantial given many moderate-to-severe patients experience poor control of their AD.[5] Patients with poorly controlled AD experience a significant burden from symptoms including poor quality sleep, reduced activities and work performance, and a high rate of mental health comorbidity,[5] further highlighting the need for adequate therapeutics. Until recently, choices of therapy outside of systemic immune suppressants were nonexistent. We are experiencing a new era of discovery in the pathogenesis of AD and, consequently, witnessing biologic and small molecule therapeutic innovation. The objective of this review is to highlight the current and near-future biologic and small molecule systemic therapeutics under investigation for AD. Armed with these new and emerging therapies, clinicians will be better suited to treat challenging and refractory AD cases.

DIAGNOSIS

The diagnosis of AD is primarily made through clinical assessment with laboratory and histopathologic findings contributing to diagnosis in difficult cases. The established diagnostic criteria by Hanifin and Rajka in 1980 are still widely used in clinical trials, and many derivations of the criteria exist with varying levels of validity.[6,7] A more clinician-friendly set of criteria based on the Hanifin-Rajka criteria were developed by the American Academy of Dermatology but require further validation.[8] Many types of dermatitis have a similar appearance to AD and should be considered in the differential diagnosis. In infants, it is often challenging to distinguish AD from seborrheic dermatitis, and various conditions such as serious nutritional deficiencies, metabolic disorders, and inborn errors of immunity that mimic the clinical features of AD.[9] Failure to thrive and noncutaneous infections are important clues to these more rare disorders and away from AD. In adults, contact dermatitis, nummular dermatitis, and cutaneous T-cell lymphoma should be considered in the differential diagnosis of AD.[9] Facial erythema after topical corticosteroid (TCS) use may also confound the clinical picture and make accurate diagnosis difficult.[10]

AD and allergic contact dermatitis (ACD) have similar characteristics and may coexist. It is essential to differentiate the 2 as they differ in prognosis and treatment. Patch testing may aid in differentiation in challenging cases.[11,12] If the dermatitis is refractory to topical therapy, patch testing may also be considered before starting systemic immunosuppression therapy. Another use of patch testing is for instances when disease worsens during treatment or recovers rapidly on discontinuation of treatment. The induction of ACD by topical treatment may be suspected, and can be confirmed through patch testing.

IDENTIFYING PATIENTS FOR SYSTEMIC THERAPY

Several studies show that subjective patient-reported symptoms are better associated with changes in quality of life than objectively measured signs in patients with AD.[13] This demonstrates the importance of a comprehensive view when treating AD that includes both clinician and patient input. The Harmonization of Eczema Outcome Measurements (HOME) initiative, an international consensus group, completed a recommended core outcome set of instruments to be included in all trials in AD. The HOME initiative recently recommended valid instruments feasible for *clinical practice* to measure patient symptoms and AD control (Table I).[14-22] These instruments are feasible to implement in a busy clinical practice and aid the

TABLE I. The HOME initiative recommends valid instruments for clinical practice to measure patient symptoms and AD control

	Tools	Reference of consensus statement
Clinical signs	Eczema Area and Severity Index (EASI) is a validated scoring system that grades the physical signs of atopic dermatitis/eczema	15
Patient-reported symptoms	Patient-Oriented Eczema Measure (POEM) is a validated instrument that measures the illness as experienced by the patient Numerical Rating Scale (NRS) 11 point (0-10) for worst itch over the last 24 hours	16, 17
Quality of life	The Dermatology Life Quality Index (DLQI) The Children's Dermatology Life Quality Index (CDLQI) The Infants' Dermatitis Quality of Life Index (IDQOL)	18, 19
Long-term control	Recap of atopic eczema (RECAP) or the Atopic Dermatitis Control Test (ADCT) for long-term control	20, 21, 22, 23

AD, Atopic dermatitis; *HOME*, Harmonizing Outcome Measurement for Eczema.

clinician in understanding the status of a patient's disease control facilitating the shared decision-making process. An international consensus conference of AD experts agreed that one scoring system cannot accurately define if a patient is eligible for systemic therapy. Instead, the need for systemic therapy is determined by a failure of appropriate topical therapy.[23] The International Psoriasis Council has recently adopted a similar approach for assessing psoriasis severity.[24]

MANAGEMENT GUIDELINES FOR MODERATE-TO-SEVERE DISEASE

Treatment guidelines vary slightly from country to country, but most list phototherapy, cyclosporine (CsA), methotrexate, azathioprine, and mycophenolate mofetil as possible therapies for those who fail topical therapy.[25] Except for the European guidelines, all were published before the approval of dupilumab in 2017.[26] Dupilumab was approved for AD in adults in 2017, adolescents in 2019, and children greater than 5 years of age in 2020 in the United States.[27] Studies of dupilumab in even younger children are underway. Future guidelines should be updated to incorporate new targeted therapies such as biologics and small molecules.[28,29] At this point, given the paucity of head-to-head trials, there is no defined systemic therapy algorithm and the choice of the first-line agent involves a shared decision-making process that incorporates patient preferences, medical assessment of comorbidities and risk stratification, and a discussion of the benefits, risks, and costs of available therapies. A consensus article consisting of dermatologists and allergists in 2017 funded by the American College of Allergy, Asthma, and Immunology agreed that dupilumab provides a more effective and safe approach to AD systemic therapy than traditional immunosuppressants.[30]

EMERGING SYSTEMIC TREATMENT: BIOLOGICS AND SMALL MOLECULES

Biologic agents are injectable protein-based therapies such as monoclonal antibodies that target cytokine receptors or soluble cytokines. Unlike biologic agents, small molecules are usually made by chemical synthesis to produce conventional pharmacological chemicals.[31] Small molecules can be formulated for topical or oral administration and often target intracellular pathways. Biologic and small molecule therapies may be useful in reducing side effects compared with broader traditional systemic immunosuppressive agents as they allow for more selective suppression of immune pathways. Janus kinase (JAK) inhibitors block signaling that occurs on activation of a variety of cytokine receptors.[31] JAK inhibitors provide the promise of an oral approach to AD therapy with flexible dosing strategies that should not lead to immunogenicity that may occur with biologic therapies over time.[31] Table II summarizes the differences in characteristics and properties between biologic therapeutic agents and JAK inhibitors.

Biologics

The central role of type 2 inflammation in AD pathogenesis has been known for more than 30 years. Abnormal IL-4 and IL-13 gene expression by T lymphocytes is reflected in altered nuclear protein interactions with IL-4 and IL-13 transcriptional regulatory elements in AD.[32,33] In addition to promoting type 2 inflammatory responses, IL-4 and IL-13 negatively impact the integrity of the epidermal barrier by inhibiting the expression of major structural proteins including filaggrin, loricrin, and involucrin.[34-36] Early approaches to inhibiting the type 2 pathway involved therapeutic administration of the type 1 cytokine IFNγ in attempts to restore the type1:type 2 balance. Although some patients benefitted from this IFNγ treatment, an unpublished phase 3 study did not meet study endpoints.[37] Recent research challenges the traditional AD pathogenesis paradigm of exclusive Th2 dominance, uncovering additional roles of several different immune pathways. Type 1, type 22, and type 17 pathway activation (including related cytokines/chemokines) have been found in the skin and blood of patients with AD, especially those with moderate-to-severe disease.[38-42] IL-22 induces epidermal proliferation and a marked increase in the terminally differentiated S100 gene at the onset of acute AD, leading to lichenification.[36] Data on the therapeutic biologics in AD are summarized in Table III.

IL-4 and IL-13 inhibition: dupilumab

IL-4 and IL-13 play essential roles in the differentiation of T helper (Th) 2 cells. In particular, IL-4 acts on Th0 cells to promote differentiation and growth of Th2 cells. Because proliferating Th2 cells produce more IL-4, they act as positive feedback to amplify and sustain the Th2 response.[41,42] The IL-4 receptor is expressed on T cells, B cells, and macrophages, and induces activation of signal transducer and activator of transcription (STAT) 6 and increases IgE production when bound by agonists. Cell culture experiments demonstrated that key barrier proteins such as filaggrin are expressed through keratinocyte differentiation. When IL-4 and IL-13 are present in abnormal levels during differentiation, filaggrin expression is reduced. Even

TABLE II. Comparison of properties of biologics and small molecules

	Biologics	Small molecules
Molecular weight	Generally >2-5 kDa	Generally <0.5 kDa
General characteristics	• Engineered monoclonal antibody • May not be a well-defined structure • Usually made with the aid of or from live cells and organisms • Often not stable; usually heat sensitive • Catabolized to amino acids, sugars, lipids, etc. • Limited toxicity • Do not penetrate cells and cross the blood-brain barrier	• Chemical compound • Well-defined structure • Usually, organic molecules prepared by chemical synthesis • Usually stable • Metabolism by liver enzymes such as cytochrome P450 • May lead to toxicity • Cross the blood-brain barrier (especially lipid-soluble)
Route of administration	Parenteral	Oral
Half-life	Long half-life (days to weeks) Allow infrequent dosing	Short half-life Require frequent dosing
Specificity for target	High selectivity and specificity for target	Higher potential for off-target effects
Immunogenicity	Possible immunogenicity	Unlikely immunogenic
Cost	High cost of development	High cost, but often lower than a biologics

after differentiation, cells exposed to IL-4 and IL-13 demonstrated suppressed filaggrin expression. This study suggests that some patients with AD have loss of filaggrin due to the Th2 inflammatory pathway.[34] These Th2 cytokines also inhibit production of barrier lipids and antimicrobial peptides.[56,57] IL-4 and IL-13 also induce expression of thymic stromal lymphopoietin (TSLP), which amplifies the Th2 activation response, and leads to OXO-40L expression on the surface of activated dendritic cells (DCs). In particular, IL-13 appears to be one of the central cytokines in AD pathophysiology.[41] A recent transcriptomic study comparing AD and psoriatic skin found that fewer than half of lesional AD skin samples expressed detectable *IL4*, with overall low expression levels. *IL13*, however, was the most predominantly expressed mRNA in AD.[33] It remains unclear how relative cytokine expression impacts pathophysiology and clinical presentation of AD. Although *IL-13* expression may be increased in lesional skin compared with *IL-4*, this alone does not drive clinical presentation or predict responses. Understanding the importance of blocking both IL-4 and IL-13 compared with blocking IL-13 alone is likely not fully possible without human trials using both approaches. The blockade of IL-4 may be more relevant to improvement in allergic comorbidities given the positive clinical effects of combined IL-4/IL-13 blockade on asthma that have not been fully realized with IL-13 blockade alone.

Dupilumab is a human monoclonal antibody (mAb) that binds the IL-4 receptor α subunit, a subunit shared between IL-4 and IL-13 cytokine receptors.[43,44] By binding the IL-4Rα subunit, dupilumab blocks both IL-4 and IL-13 signaling and their downstream effects. Two randomized, placebo-controlled phase 3 trials (SOLO 1 and SOLO 2) determined the efficacy and safety of dupilumab in adults with moderate-to-severe AD.[43,44] The primary outcome of clear or almost clear skin was achieved by 36% to 38% of all patients who received dupilumab compared with 8% to 10% in patients who received placebo ($P < .0001$).[58] Additional *post hoc* analyses found clinically relevant reductions in disease severity and symptoms even in the majority of patients who did not achieve this stringent endpoint.[58] The mechanism of action studies of dupilumab showed that although Th2 biomarkers were inhibited with dupilumab (ie, CCL17, CCL18, CCL26), Th17/Th22 biomarkers (PI3, S100As) were also significantly downregulated, but with no significant modulation of the Th1 axis.[59,60] A large biomarker study using proteomic analysis of tape-stripped epidermal layers (strata corneum and granulosum) showed a reduction in general inflammatory markers, Th2 and Th17/Th22 inflammatory proteins in lesional skin after treatment with dupilumab. These reductions were not observed to this degree in nonlesional skin. Further analysis demonstrated a significant association between reductions in inflammatory proteins and clinical improvement in AD (by percentage improvement of Eczema Area and Severity Index [EASI]). This biomarker study demonstrated the importance of type 2 cytokines in driving the broader inflammatory profile observed in these patients.[61] Furthermore, tape stripping may serve as a relative noninvasive technique to study the biology of the skin in AD and potentially serve as a platform for biomarker discovery.

In the CHRONOS study, 740 adults with moderate-to-severe AD were randomized to dupilumab or placebo with both arms using concomitant topical therapy, unlike the SOLO monotherapy studies. The safety and efficacy results after 16 weeks were similar to those of the SOLO study. The results were proven to be stable over the 52-week study.[26] Another phase 3 trial, the CAFÉ study, studied patients previously exposed to CsA or patients with undesirable or contraindication CsA response. Significantly more patients in the dupilumab qw (every week) + TCS and q2w (every 2 weeks) + TCS groups achieved ≥75% improvement from baseline in the EASI at week 16 versus the placebo + TCS group (primary endpoint) (59.1% and 62.6% vs 29.6%, respectively; $P < .001$ vs placebo + TCS, both doses).[28] The CAFÉ study demonstrated dupilumab effectiveness in a potentially highly refractory patient population. More recently, dupilumab significantly improved the signs and symptoms of AD in adolescent patients with moderate-to-severe disease and in severe pediatric AD in children between the ages of 6 and 11.[62,63] Studies in younger age groups are ongoing.

In clinical trials, patients with AD treated with dupilumab had a greater incidence of conjunctivitis (8.6%-22.1%) than placebo-treated patients (2.1%-11.1%).[64] Most cases were mild to moderate and patients fully recovered (or were recovering during

TABLE III. New systemic biologics; targeted therapies of AD

	Target	Clinical study	Primary endpoint: efficacy	Duration/combination Tx.	Adverse effect*
Dupilumab	IL-4Rα	Phase 3[43,44] (SOLO1, 2)	EASI-75: 48%	16-wk monotherapy	Conjunctivitis
		Phase 3[26] (CHRONOS)	EASI-75: 64%	52 wk with TCS	Conjunctivitis
		Phase 3[28] (CAFÉ)	EASI-75: 64%	16 wk with TCS	Conjunctivitis
Tralokinumab	IL-13	Phase 3[45] (ECZTRA1, 2)	IGA 0/1 achievement: 15.8% vs 7.1% in ECZTRA 1 (difference [95% CI] 8.6% [4.1-13.1]; $P = .002$) 22.2% vs 10.9% in ECZTRA 2 (11.1% [5.8-16.4]; $P < .001$) EASI-75: 25.0% vs 12.7% in ECZTRA 1 (12.1% [6.5-17.7]; $P < .001$) 33.2% vs 11.4% in ECZTRA 2 (21.6% [15.8-27.3]; $P < .001$)	52-wk monotherapy	Upper respiratory tract infection, skin infection, conjunctivitis
		Phase 3[46] (ECZTRA3)	IGA 0/1 achievement: 38.9% vs 26.2% (difference [95% CI] 12.4% [2·9-21·9]; $P =$ ·015) EASI-75: 56.0% vs 35.7% (20.2% [9·8-30.6]; $P < .001$)	16 wk with TCS	Upper respiratory tract infection, skin infection, conjunctivitis
Lebrikizumab	IL-13	Phase 2a[47] (TREBLE)	EASI-50: 82.4%	12 wk with TCS	Upper respiratory tract infection, nasopharyngitis, headache, injection site reactions, herpesvirus infections, conjunctivitis
		Phase 2b[48]	EASI reduction: 125 mg, q4 weeks: 62.3% 250 mg, q4 weeks: 69.2% 250 mg q2 weeks: 72.1%	With TCS	Upper respiratory tract infection, nasopharyngitis, injection-site pain
Etokimab	IL-33	Phase 2a[50]	EASI-50: 83.3%	140 d	Headache
		Phase 2b[51] (ATLAS)	EASI-50: failed to meet primary endpoint		
Nemolizumab	IL-31	Phase 2a	VAS change: 0.1/0.5/2.0 mg/kg: 43.7/59.8/63.1%	12 wk with TCS	Upper respiratory tract infection, nasopharyngitis, peripheral edema, increased creatine kinase levels
		Phase 2b[52]	VAS change: 0.1/0.5/2.0 mg/kg (q4 weeks): 73.0/89.6/74.7% 2.0 mg/kg (q8 weeks): 79.1%	24 wk with TCS	Upper respiratory tract infection, nasopharyngitis, peripheral edema, increased creatine kinase levels
		Phase 3	VAS change: −42.8% vs −21.4% EASI score change: −45.9% vs −33.2%	16 wk with TCS	Injection-site reaction
Tezepelumab	TSLP	Phase 2a[53]	EASI-50: 64.7%	12 wk with TCS	Injection-site erythema
GBR830	OX40	Phase 2a[54]	Improved epidermal pathology	4 wk	Nasopharyngitis
Fezakinumab	IL-22	Phase 2a[55]	SCORAD change: at 12 wk† 13.8 ± 2.7 vs 21.6 ± 3.8 at 20 wk† 27.4 ± 3.9	12 wk with TCS	Upper respiratory tract infection

AD, Atopic dermatitis; *CI*, confidence interval; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *TCS*, topical corticosteroid; *TSLP*, thymic stromal lymphopoietin; *VAS*, visual analog score.
*Only above than control group.
†Severe SCORAD subset.

study treatment); study treatment discontinuation due to conjunctivitis was rare.[65-67] Since regulatory approval, case reports confirm conjunctivitis in patients with AD with real-world use of dupilumab, with some centers reporting as high as 34% prevalence after 16 weeks of use.[64] Ocular symptoms reported include conjunctival redness, blepharitis, eye dryness, irritation,

discharge, itching, stinging, burning, tearing, foreign-body sensation, blurred vision, and ectropion.[65-67] Rare serious eye events have also been reported.[68] Most cases of conjunctivitis can be managed with topical anti-inflammatory therapy and the dupilumab therapy is continued. Interestingly, in patients with asthma or nasal polyposis, the incidence of conjunctivitis was not higher than that of placebo.[43,44,58-60,65,66] This suggests that conjunctivitis may not be an intrinsic effect of dupilumab, but possibly a specific disease-drug interaction.

IL-13 inhibition: tralokinumab

The IL-13 receptor family (IL-13R) includes IL-13Rα1 and IL-13Rα2. IL-13Rα2 has a short cytoplasmic tail that differs from IL-13Rα1, has no known signaling motif, and is thought to possibly regulate IL-13 levels through internalization of IL-13.[69,70] Tralokinumab is a humanized IgG4κ anti-IL-13 mAb derived from a human phage display library that blocks IL-13 from binding to IL-13Rα1 and IL-13Rα2, resulting in a lack of IL-13 receptor signaling via blocking IL-4Rα/IL-13Rα1 heterodimerization (type 2 receptor). It prevents downstream IL-13-mediated signaling and may alter endogenous regulation of IL-13 mediated by IL-13Rα2.

In 2 randomized, double-blind, placebo-controlled, phase 3 trials, ECZTRA 1 and ECZTRA 2, adults with moderate-to-severe AD injected subcutaneous tralokinumab 300 mg every 2 weeks. Primary endpoints were Investigator's Global Assessment (IGA) score of 0 or 1 (0/1) at week 16 and EASI change at week 16. Tralokinumab achieved an IGA score of 0/1: 15.8% (vs placebo, 7.1%) in ECZTRA 1 (difference [95% confidence interval (CI)] 8.6% [4.1-13.1]; $P = .002$) and 22.2% (vs placebo, 10.9%) in ECZTRA 2 (11.1% [5.8-16.4]; $P < .001$) and EASI-75: 25.0% versus 12.7% (12.1% [6.5-17.7]; $P < .001$) and 33.2% versus 11.4% (21.6% [15.8-27.3]; $P < .001$). The results showed that tralokinumab monotherapy was superior to placebo at 16 weeks of treatment and was well tolerated up to 52 weeks of treatment. The majority of adverse effects (AEs) were nonserious with most resolved or resolving by the end of the treatment period. The most frequently reported AEs were upper respiratory tract infection and conjunctivititis.[45]

The ECZTRA 3 study was a double-blind, placebo plus optional TCS-controlled phase 3 trial. Patients were randomized 2:1 to subcutaneous tralokinumab 300 mg or placebo every 2 weeks with TCS as needed over 16 weeks. At week 16, tralokinumab-treated patients achieved IGA 0/1: 38.9% (vs 26.2%) (difference [95% CI]: 12.4% [2.9-21.9]; $P = .015$) and EASI-75: 56.0% (vs 35.7%) (20.2% [9.8-30.6]; $P < .001$).[46]

IL-13 inhibition: lebrikizumab

Lebrikizumab is a humanized IgG4κ mAb that binds soluble IL-13 and acts through selective inhibition of the IL-4Rα/IL-13Rα1 signaling complex. However, lebrikizumab does not prevent binding to IL-13Rα2, and thus endogenous regulation of IL-13 levels remains intact.

In a phase 2 randomized, double-blinded study (TREBLE), lebrikizumab's safety and efficacy were assessed in patients with moderate-to-severe AD for 12 weeks combined with required twice-daily TCS. At 12 weeks, the group receiving lebrikizumab 125 mg every 4 weeks reached EASI-50 at a greater rate than the group receiving placebo every 4 weeks (82.4% vs 62.3%; $P = .026$).[47] In a phase 2b study, the following 4 groups were studied: placebo, 125 mg every 4 weeks, 250 mg every 4 weeks, and 250 mg every 2 weeks. Higher dosages and more frequent dosing were more effective.[48] EASI scores improved for patients on lebrikizumab 125 mg every 4 weeks (62.3%), 250 mg every 4 weeks (69.2%), and 250 mg every 2 weeks (72.1%). All 3 groups improved significantly compared with the placebo group (41.1%).[48] Reported AEs included upper respiratory tract infection (7.5% vs 5.8% for placebo), nasopharyngitis (6.6% vs 3.8% for placebo), and injection site pain (3.1% vs 1.9% for placebo).[48] Phase 3 studies are underway.

IL-33 inhibition: etokimab

With technological advancements and an increased understanding of AD pathophysiology, new cytokines have emerged as key players in inflammatory skin diseases. IL-33 is an alarmin cytokine, quickly released from an array of cell types after cellular stress such as inflammation, infection, or other damage. IL-33 interacts with the ST2/IL-1RAcP receptor complex to initiate NF-kB and MAP kinase that ultimately lead to type 2 inflammation. Most notably, this results in increased IL-5 and IL-13. This mechanism of inflammation influences a myriad of inflammatory diseases including AD, asthma and inflammatory bowel disease, and rheumatoid arthritis.[49]

Etokimab (ANB020) is a human IgG1 mAb that directly binds IL-33 and prevents receptor signaling, thereby decreasing downstream Th2 inflammation.[50] It also reduces neutrophil infiltration and inhibits migration to the skin in a CXCR1 (CXC chemokine ligand 1)/IL-8−dependent manner.[50]

In a phase 2a study of etokimab without a placebo control, 12 adult patients with moderate-to-severe AD received etokimab for 140 days. Eighty-three percent of patients achieved EASI-50, and 33% achieved EASI-75, with a reduction in peripheral eosinophils at day 29 after administration, and no identifiable drug-related safety signals. However, in a phase 2b randomized, double-blinded placebo-controlled study (ATLAS), the study failed to meet the primary endpoint of the trial.[51]

IL-31 inhibition: nemolizumab

The mechanics of scratching and subsequent microabrasions in the skin barrier promote entry of allergens and microbes, leading to the "itch-scratch cycle," a major contributor to AD exacerbations.[51] Transient receptor potential cation channel vanilloid subtype 1 (TRPV1)+ and a subpopulation of TRPV1+/transient receptor channel potential cation channel ankyrin subtype 1 (TRPA1)+ sensory neurons are thought to be required for pruritogen-induced itch signaling.[71]

IL-31 is a proinflammatory cytokine thought to be a primary driver of pruritus in AD. IL-31 signaling occurs through a heterodimeric receptor composed of the oncostatin M receptor (OSMR) and IL-31 receptor α (IL-31RA) subunit. IL-31RA and OSMR are elevated in the afferent cutaneous nerve fibers and dorsal root ganglia in patients with AD.[72]

IL-31RA is a functional receptor expressed by a small subpopulation of IL-31RA+/TRPV1+/TRPA1+ neurons and is a critical neuroimmune link between TH2 cells and sensory nerves for the generation of T-cell−mediated itch. Thus, targeting neuronal IL-31RA might be effective in the management of AD.[71,73]

Nemolizumab is a humanized mAb that targets anti-IL31RA, which mediates IL-31 signaling when coupled with OSMR.[74] In phase 2 long-term extension studies, the authors reported the long-term efficacy and safety of nemolizumab injected every 4 weeks or 8 weeks for 52 weeks.[74,75] A randomized and

double-blind phase 2b clinical study determined that the 30 mg dose was most effective at all endpoints, including percentage change from baseline EASI, IGA, and peak pruritus numeric rating scales (NRS) scores at weeks 16 and 24. At 30 mg, nemolizumab reduced EASI scores by 68.8% versus 52.1% in placebo over 24 weeks ($P = .016$), IGA responses (IGA 0/1) were greater at week 16 compared with placebo (33.3% vs 12.3%, $P = .008$). NRS response rates (4-point decrease) were also greater at weeks 16 and 24.[75] Nemolizumab was well tolerated across all dose levels in this trial.

A 16-week, double-blind, phase 3 trial enrolled Japanese patients with AD and moderate-to-severe pruritus. Patients received subcutaneous nemolizumab (60 mg) or placebo in a 2:1 ratio every 4 weeks until week 16, with concomitant topical agents. At week 16, the mean percent change in the visual analog pruritus score was −42.8% in the nemolizumab group and −21.4% in the placebo group (difference, −21.5 percentage points; 95% CI, −30.2 to −12.7; $P < .001$). The mean percent change in EASI was −45.9% with nemolizumab and −33.2% with placebo. The incidence of injection-related reactions was 8% with nemolizumab and 3% with placebo.[52]

IL-31 inhibition: KPL-716

KPL-716 is an anti-oncostatin M receptor beta mAb (anti-OSMRβ) that inhibits IL-31. KPL-716 showed good safety and tolerability as well as an antipruritic effect in patients with moderate-to-severe AD in a phase1a/1b study.[76] Additional phase 2 studies (NCT03858634, NCT03816891) for chronic pruritic diseases and prurigo nodularis are underway.

TSLP inhibition: tezepelumab

TSLP, an epithelial cell-derived cytokine, is produced in response to proinflammatory stimuli. TSLP plays a vital role in triggering the downstream cascade of Th2 inflammation in asthma and AD.[77] Tezepelumab (AMG 157/MEDI9929) is a fully human immunoglobulin G2k mAb that inhibits TSLP, which is thought to inhibit TSLP-dependent itch, atopic inflammation, and Th2 inflammation.[77]

In a phase 2a randomized, double-blind, and placebo-controlled study (ALLEVIAD), the safety and efficacy of tezepelumab was assessed in patients with moderate-to-severe AD. By week 12, patients treated with tezepelumab did not achieve significant improvements in EASI-50 compared with placebo-treated patients (64.7% vs 48.2%; $P = .091$). Secondary outcome measures including EASI-75, EASI-90, SCORing Atopic Dermatitis (SCORAD), and NRS at weeks 12 and 16 showed no statistically significant improvement as well.[77]

The lack of clinically significant results is somewhat surprising given positive results with tezepelumab in asthma trials.[53] Excessive use of TCS permitted in this AD study may have confounded results; future monotherapy studies are needed.

OX40 inhibition: GBR830

OX40 (CD134) binds to OX40 ligand (OX40L; CD252) found on antigen-presenting cells. OX40-OX40L is thought to bridge Th2 and Th1 pathways by inducing IFNγ secretion and causing autoreactive T cells to acquire effector T-cell function. In patients with AD, the number of $OX40L^+$ DCs is highly increased.[78]

GBR 830 is a human IgG1 mAb specific to OX40 (CD 134), a costimulatory receptor expressed on T cells that are thought to potentiate T-cell responses. In a phase 2a randomized, double-blind, and placebo-controlled study, the safety and efficacy of GBR 830 was assessed in patients with moderate-to-severe AD, affected body surface area of >10%, EASI >12, and an inadequate response to topical treatments. Two doses of GBR830 administered 4 weeks apart were well tolerated. The proportion of patients achieving EASI-50 was greater with GBR 830 (76.9%) than placebo (37.5%). Biopsy of lesional skin showed significantly reduced epidermal hyperplasia at day 71 with GBR830.[79]

OX40 inhibition: KHK4083

KHK4083 is a humanized mAb against OX40. In a phase 1, single-center, open-label, repeated-dose study, 22 patients received KHK4083 10 mg/kg IV on day 1, day 15, and day 29, and were followed until day 155. Continued improvement in EASI and IGA was seen throughout the study, and the changes in thymus and activation-regulated chemokine continued to decrease until study day 155.[54]

IL-22 inhibition: fezakinumab

IL-22, an α-helical cytokine of the IL-20 subfamily, is strongly upregulated in patients with AD and acts as a proinflammatory cytokine that, in synergy with IL-17, triggers upregulation of antimicrobial peptides.[80] It is considered the main driver of epidermal hyperplasia in AD, promoting keratinocyte proliferation and inhibiting terminal differentiation.[80,55]

Fezakinumab (ILV-094) is a human IgG1-lambda type mAb that directly binds to IL-22 and inhibits IL-22 binding to the extracellular domain of IL-10 receptor 2 (IL-10R2), blocking downstream signaling.[80] In a phase 2a randomized, double-blind, and placebo-controlled study, the mean decline in SCORAD was 13.8 ± 2.7 with fezakinumab and 8.0 ± 3.1 with placebo at 12 weeks ($P = .134$). However, in the severe subset of patients, improvement in IGA was significantly greater with fezakinumab than placebo (0.7 ± 0.2 vs 0.3 ± 0.1; $P = .034$). Upper respiratory tract infection was overall the most common AE, but the incidence was not significantly different than placebo.[80] Patients were stratified by their baseline *IL-22* mRNA expression. Those with higher baseline *IL-22* expression responded to fezakinumab, whereas those with below median *IL-22* expression did not. This study is the first example of personalized medicine for AD treatment that incorporates biomarkers.[81]

Small molecules

Table IV summarizes therapeutic small molecules under development for AD.

JAK inhibitors

JAK inhibitors bind the kinase component of JAKs, prevent phosphorylation, and inhibit transduction of intracellular STAT pathways. Because of the heterogeneous cytokine expression involved in AD, inhibiting the JAK/STAT pathways is an attractive treatment target to improve outcomes. Chronic itching relies on neuronal JAK1 signaling, and JAK inhibition appears to directly block neuronal transmission of itch.[90] Chronic itch is dependent on neuronal IL-4Rα and JAK1 signaling, and patients with recalcitrant chronic itch who failed other immunosuppressive therapies have markedly improved when treated with JAK inhibitors.[90] JAK-STAT blockade may also impact eosinophil activation, B-cell maturation, epidermal chemokines, and numerous other pathways of AD pathophysiology. The use of

TABLE IV. New systemic small molecules; targeted therapies of AD

	Target	Study type	Primary endpoint: efficacy	Duration/combination Tx.	Adverse effect*
Upadacitinib	JAK1	Phase 2b[82]	7.5/15/30 mg vs placebo EASI reduction: 39.4/61.7/74.4% vs 23.0% NRS: 39.6/48.0/68.9% vs 9.7% EASI-75: 28.6/52.4/69.0% vs 9.8%	16 wk with TCS	Upper respiratory tract infection, appendicitis, pericoronitis, skin infection
Abrocitinib	JAK1	Phase 2b	IGA (0/1) achievement: 44% (200 mg) vs 6% (placebo)	12 wk with TCS	Eczema herpeticum, pneumonia
		Phase 3[83] (JADE MONO-1)	200/100 mg vs placebo IGA (0/1) achievement: 43.8/23.7% vs 7.9 EASI-75: 63/40% vs 12%	12 wk with TCS	Nausea, nasopharyngitis
		Phase 3[84] (JADE MONO-2)	200/100 mg vs placebo IGA (0/1) achievement: 38.1/28.4% vs 9.1 EASI-75: 61.0/44.5% vs 10.4%	12-wk monotherapy	Decreases in platelet count, thrombocytopenia
Baricitinib	JAK1/2	Phase 2a[78]	2/4 mg vs placebo EASI reduction: 65% vs 46% Significant improvement in pruritus and sleep loss, QoL	16 wk with TCS	Neutropenia, abnormal lymphocyte count, headache, eczema, benign polyp of the large intestine
		Phase 3[85] (BREEZE)	2/4 mg vs placebo IGA (0/1) achievement: 31/24% vs 15%	16 wk with TCS	Nasopharyngitis, upper respiratory tract infection, folliculitis
Tofacitinib	JAK1/3	Case series[86]	5 mg Decrease in SCORAD for all patients	14 wk	None
Gusacitinib	Pan JAK	Phase 1b[87]	20/40/80 mg vs placebo EASI-50: 20/100/83% vs 22% EASI-75: 0/71/63% vs 22% NRS change: -1.3 ± 2.1, -3.1 ± 2.7, -4.7 ± 2.1 vs -1.6 ± 1.8	14 wk with TCS	Headache, nausea, diarrhea, nasopharyngitis, back pain, hypertension, low lymphocyte levels
Apremilast	PDE-4	Phase 2[88]	30/40 mg vs placebo EASI reduction: 31.6% vs 11.0%	12 wk with TCS	Cellulitis
JNJ-39758979	H4	Phase 2a[89]	Failed to meet primary endpoint	6 wk	None

AD, Atopic dermatitis; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; JAK, Janus kinase; *NRS*, numeric rating scales; *PDE-4*, phosphodiesterase enzyme 4; *QoL*, quality of life; *SCORAD*, SCORing Atopic Dermatitis; *TCS*, topical corticosteroid.
*Only above than control group.

JAK inhibitors has the advantage of possibly targeting and treating several immune-mediated diseases.[91]

Selective JAK1 inhibition: upadacitinib

Upadacitinib is an oral selective JAK1 inhibitor that is under investigation for moderate-to-severe AD in adolescents and adults. It is currently approved for the treatment of rheumatoid arthritis. A recent phase 2b study found a 74% reduction in EASI compared with 23% in placebo at 16 weeks.[92] Half of the participants treated with 30 mg achieved an EASI-90 and IGA of 0/1. All upadacitinib doses (7.5, 15, and 30 mg) showed significantly higher mean percentage improvement from baseline at week 16 in EASI versus placebo (39%, $P = .03$; 62%, $P < .001$; and 74%, $P < .001$ vs 23%, respectively), with a clear dose-response relationship. Mean (95% CI) difference versus placebo for percentage improvement from baseline at week 16 in EASI was 16% (1.4%-31%), 39% (24%-54%), and 51% (36%-67%), for upadacitinib 7.5, 15, and 30 mg, respectively.[92] AEs were reported in 71% (30 of 42), 74% (31 of 42), and 79% (33 of 42) of patients receiving upadacitinib 7.5, 15, and 30 mg, respectively, versus 63% (25 of 40) of placebo, with no relationship to the dose of upadacitinib.[92] The most frequently reported AEs were upper respiratory tract infection, AD worsening, and acne.[92]

Recently, a press release reported results for the phase 3 Measure Up 1 and Measure Up 2 studies for upadacitinib in AD. The results showed a greater improvement in measures of skin clearance including the EASI score and IGA and a reduction in itch with upadacitinib monotherapy (15 or 30 mg; once daily) compared with placebo.[83]

Selective JAK1 inhibition: abrocitinib

Abrocitinib is an oral JAK1 selective inhibitor under investigation for the treatment of AD. A phase 3 trial (MONO-1) showed that the proportion of patients who achieved IGA 0/1 was 43.8% for abrocitinib 200 mg (n = 154), 23.7% for abrocitinib 100 mg (n = 156), and 7.9% for placebo (n = 77) at 16 weeks.[83] At week 12, the proportion of patients who had achieved an EASI-75 was 40% in the abrocitinib 100 mg group (vs 12% in the placebo group, $P < .0001$) and 63% in the abrocitinib 200 mg group ($P < .0001$).[83] In the abrocitinib groups, frequently reported AEs not seen in placebo were nausea and nasopharyngitis.[83] In other phase 3 clinical trial (MONO-2) of 391 patients 12 years or older with moderate-to-severe AD, significantly greater proportions of patients treated with abrocitinib (200 or 100 mg) achieved an IGA response 0/1) with improvement of at least 2 grades.[84] At week 12, greater proportions of patients in the 200- and 100-mg abrocitinib groups achieved an IGA response compared with placebo (59 of 155 [38.1%] and 44 of 155 [28.4%] vs 7 of 77 [9.1%]; $P < .001$) and EASI-75 (94 of 154 [61.0%] and 69 of 155 [44.5%] vs 8 of 77 [10.4%]; $P < .001$).[84] Decreases in platelet count (2 [1.3%]) and thrombocytopenia (5 [3.2%]) were reported in the 200-mg group.[84]

JAK 1/2 inhibition: baricitinib

Baricitinib is a selective JAK1 and JAK2 inhibitor that is approved for the treatment of rheumatoid arthritis. A randomized, double-blind, placebo-controlled phase 2 study of adults with moderate-to-severe AD treated with oral baricitinib included a 4-week TCS (triamcinolone 0.1%) run-in followed by 16 weeks of baricitinib 2 mg, 4 mg, or placebo with continued use of TCS.[78] EASI-50 responses of 62% to 68% were reported at weeks 4 and 16.[93] During this study, baricitinib patients used approximately 30% less TCS (by weight) monthly after randomization than placebo patients.[93] Improvement in pruritus began as early as week 1.[93] Regarding safety, number of headaches and elevated serum creatine kinase were greater in the baricitinib groups, and nasopharyngitis occurred in 3 to 5 patients. There was no increase in the baricitinib groups compared with placebo.[93]

In a phase 3 study (BREEZE-AD7), patients were randomly assigned (1:1:1) to receive 2 mg of baricitinib once daily (n = 109), 4 mg of baricitinib once daily (n = 111), or placebo (n = 109) for 16 weeks. The use of low-to-moderate potency TCSs was allowed. At week 16, an IGA response of 0/1 was achieved by 34 patients (31%) receiving 4 mg of baricitinib and 26 (24%) receiving 2 mg of baricitinib compared with 16 (15%) receiving placebo.[85] The most common AEs were nasopharyngitis, upper respiratory tract infections, and folliculitis.[85] Similar results have been reported for additional phase 3 studies for baricitinib.[94] Pooled safety data for baricitinib for 2247 patient-years revealed infrequent serious AEs with rare cases of eczema herpeticum with declining rates over time. There were 2 cases of pulmonary emboli although it remains unclear whether this rate is elevated above the normal population of patients with AD.[95]

JAK 1/3 inhibition: tofacitinib

In 2015, 6 patients with moderate-to-severe AD who failed standard therapy were treated with tofacitinib 5 mg once or twice daily. The mean SCORAD index decreased 54.8% at 14 weeks of treatment, and itching and sleep loss scores were also significantly reduced.[86] However, currently, the development of tofacitinib for AD has ceased, and there are no further studies.

Pan JAK/SYK inhibition: gusacitinib

Gusacitinib is a potent, dual inhibitor of JAK and spleen tyrosine kinase (SYK). In phase 1b proof-of-concept trial study, EASI-50 was achieved by nearly all patients, and EASI-75 was achieved by 63% of patients given 80 mg.[87] Skin biopsy and gene expression studies as well as blood studies[87,96] showed that gusacitinib reversed the lesional skin transcriptome toward a nonlesional phenotype.[87]

Phosphodiesterase enzyme 4 inhibition: apremilast

Phosphodiesterase enzyme 4 (PDE-4) is an essential regulator of intracellular cyclic adenosine monophosphate (cAMP) levels expressed within inflammatory cells, including T lymphocytes and eosinophils. Inhibition of PDE-4 increases the cAMP level, thereby inhibiting the production and secretion of proinflammatory cytokines and chemokines (eg, IL-2, IL-4, IL-31) that are thought to contribute to the expression of AD.[88]

Apremilast, an oral PDE-4 inhibitor, blocks inflammatory pathways; inhibits the production of TNF, IL-12, IL-2, IFNγ, IL-5, IL-8, leukotriene B4, and adhesion molecule CD18/CD11b *in vitro*, and increases the production of IL-10.[88] In a phase 2 clinical trial, patients randomly received placebo, 30 mg apremilast or 40 mg apremilast for 12 weeks. Those in the 40-mg group showed significant improvement in EASI (−31.6% vs −11.0%; $P < .04$, n = 64) and showed a decrease in Th17/22-related markers (IL17, 22 and S100A7/A8; $P < .05$).[88]

Apremilast at the 40 mg dose showed clinical efficacy and reduced Th17/Th22-related biomarkers, but the study was discontinued because of serious AEs such as cellulitis.

Histamine receptor antagonists: H4R antagonist (JNJ-39758979)

Antihistamines have long been used to treat AD-related itching, but their effectiveness is limited.[97,98] Recently, it has been confirmed that histamine H4 receptor (H4R) plays an important role in the inflammatory response. The expression of H4R by CD4+ T cells tends to be higher in patients with AD, and stimulation of the receptor leads to the upregulation of IL-31 mRNA.[97,98]

Treatment with H4R antagonists in mouse dermatitis models reduced skin lesions, infiltration of inflammatory cells, and inflammatory cytokine production, in which the H4R antagonist inhibited scratching.[99] In a 2a clinical study conducted in Japan, results did not reach the primary endpoint. Further studies should be completed to determine the safety profile in the future.[89]

SHARED DECISION MAKING

The rapid development of various AD treatments is encouraging and gives patients and clinicians additional therapeutic options. However, not all patients have the same response to

treatments or goals of care, so shared decision making is essential to find the most appropriate treatment plan. Rather than assuming that decision making should be made by scientific consensus on effectiveness, Elwyn[100] suggests the "Three-talk model of shared decision making." This emphasizes that decision sharing should play an important role in the clinician decision-making process, including informed preferences.[100] This represents a significant shift from the traditional clinician-patient dynamic. Shared decision making incorporates informed preferences—that which matters to patients and families—when shaping care plans. Team-based care, providing patients with multiple options for each decision, and considering health literacy are all ways to increase shared decision making. With an influx of new AD therapies, it will be crucial for clinicians to discuss the benefits and risks of each with patients, to help patients find the best choice for their medical comorbidities, and to understand barriers to therapy including drug cost. In the future, shared decision making may include a personalized medicine approach with treatment based on biomarker profile, further optimizing AD treatment.[101-103,61]

Until advances are made in identifying predictive biomarkers, treatment decisions will be based on patient preferences and medical profile. For example, patients who prefer rapid onset of drug effects, an oral route of administration, and dose flexibility may choose an oral JAK inhibitor if they are willing to accept the rare theoretical risks that have been observed with this class of drug. Patients with a family history of clotting disorders may want to avoid JAK inhibition due to the rare but serious risk of venous thrombosis observed with JAK inhibitor use in rheumatoid arthritis. Patients with multiple allergic comorbidities or who are risk averse may choose a biologic that targets the type 2 immune pathway. Clinicians will help inform patients which treatment options would be most appropriate given their condition, preferences, and comorbidities. This individualized treatment plan will help ensure patients receive the optimal therapy that aligns with their preferences and increases their chances for safe and effective treatment outcomes.

CONCLUSION

Limited treatment options for patients with moderate-to-severe AD have led to rapid innovation and development of novel therapeutics to help treat this chronic, relapsing inflammatory disease. What began with dupilumab has now evolved into multiple biologic and small molecule drugs that are safe and effective AD treatments, improving both disease severity and quality of life. Additional trials are underway for existing and emerging therapies that will inform future systemic treatment algorithms and help clinicians and patients determine the best course forward in the treatment of AD.

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