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LEADING ARTICLE

New and Emerging Systemic Treatments for Atopic Dermatitis

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Abstract
Atopic dermatitis (AD) is a prevalent inflammatory skin condition that, depending on its severity, can cause enormous morbidity. Corticosteroids and systemic immunosuppression, traditionally standard of care for difficult-to-treat disease, have many undesirable side effects. The desire for targeted treatments along with an improved understanding of the pathophysiology of AD has spurred the development of novel treatments. In this article, we review promising new treatments and discuss how their targets—IL-13, IL-31, OX40 (CD134), and the Janus kinase family of proteins—participate in the pathogenesis of AD. We review the published phase II and III data for dupilumab, tralokinumab, lebrikizumab, nemolizumab, anti-OX40 antibody, baricitinib, abrocitinib, and upadacitinib. The introduction of new agents may offer new options, but it remains to be seen how narrow-acting agents, like single interleukin inhibitors, will compare in safety and efficacy to broad-acting agents such as JAK inhibitors.

Key Points

Our better understanding of the pathophysiology of AD has resulted in an explosion of research into new immunotherapies for this patient population.

Multiple new agents targeting IL-13, IL-31, OX40 (CD134), and Janus kinase proteins may be effective for AD.

1 Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by pruritus and skin barrier dysfunction [1–3]. Current mainstay treatments include topical moisturizers, topical corticosteroids, topical calcineurin inhibitors, phototherapy, and systemic immunotherapies [4]. Moderate-to-severe AD is often refractory to first-line topical treatments; while systemic immunosuppressants are efficacious, they have significant adverse effects [4].

The shortcomings of mainstay treatments prompted the development of targeted topical and systemic immunotherapies involving pathways directly responsible for AD. The US Food and Drug Administration (FDA) approved a topical phosphodiesterase-4 (PDE_4) inhibitor, crisaborole, in 2016 for mild-to-moderate AD and a monoclonal antibody, dupilumab, in 2017 for moderate to severe AD [5]. While the efficacy of dupilumab is considerable, the clinical success

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of crisaborole is less impressive. Additional new treatments are desirable, as AD is a heterogeneous disease with several immunologic phenotypes [3]. The purpose of this review is to discuss the mechanisms, safety, and efficacy of the new and upcoming systemic immunologic treatments for AD.

2 Immunology of Atopic Dermatitis

Atopic dermatitis is a disease without a single identifiable pathophysiological cause [3, 6]. Several subtypes of AD exist, including extrinsic, intrinsic, pediatric-onset, and hand and foot [3, 7, 8]. These subtypes have different inciting factors and molecular compositions [7]. For example, IgE levels are only elevated in about 20–50% of patients, and loss-of-function mutations in the filaggrin (*FLG*) gene are only identified in a small subset of AD patients of European ancestry [1, 4, 9]. However, all subtypes of AD are characterized by a cycle of T cell mediated skin inflammation and disruption of the skin barrier [8, 10].

Effector immune cells are recruited to sites of skin damage when injured keratinocytes release pro-inflammatory signals. In the acute phase, type 2 helper T cells (T_H2), type 17 helper T cells (T_H17), and type 22 helper T cells (T_H22) predominate. Increased type 1 helper T cell (T_H1) activation along with T_H2 and T_H22 inflammation characterizes the chronic phase of the disease [10]. Cytokines, such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33 promote the maturation of skin resident T_H2 and group 2 innate lymphoid cells (ILC2s) [1, 4]. ILC2s are tissue-resident lymphocytes that do not derive from either the T cell or B cell lineage. Along with T_H2 cells, ILC2s produce a large amount of the pro-inflammatory cytokine IL-13 [1, 11].

When IL-4 or IL-13 binds to either type (I or II) of the IL-4 receptor complex, an associated Janus kinase (JAK) protein—JAK1, JAK2, JAK3, or tyrosine kinase 2 (TYK2)—is phosphorylated and activated (Fig. 1) [11]. Activation of JAK proteins leads to a phosphorylation cascade, which ultimately activates the transcription factors signal transducer

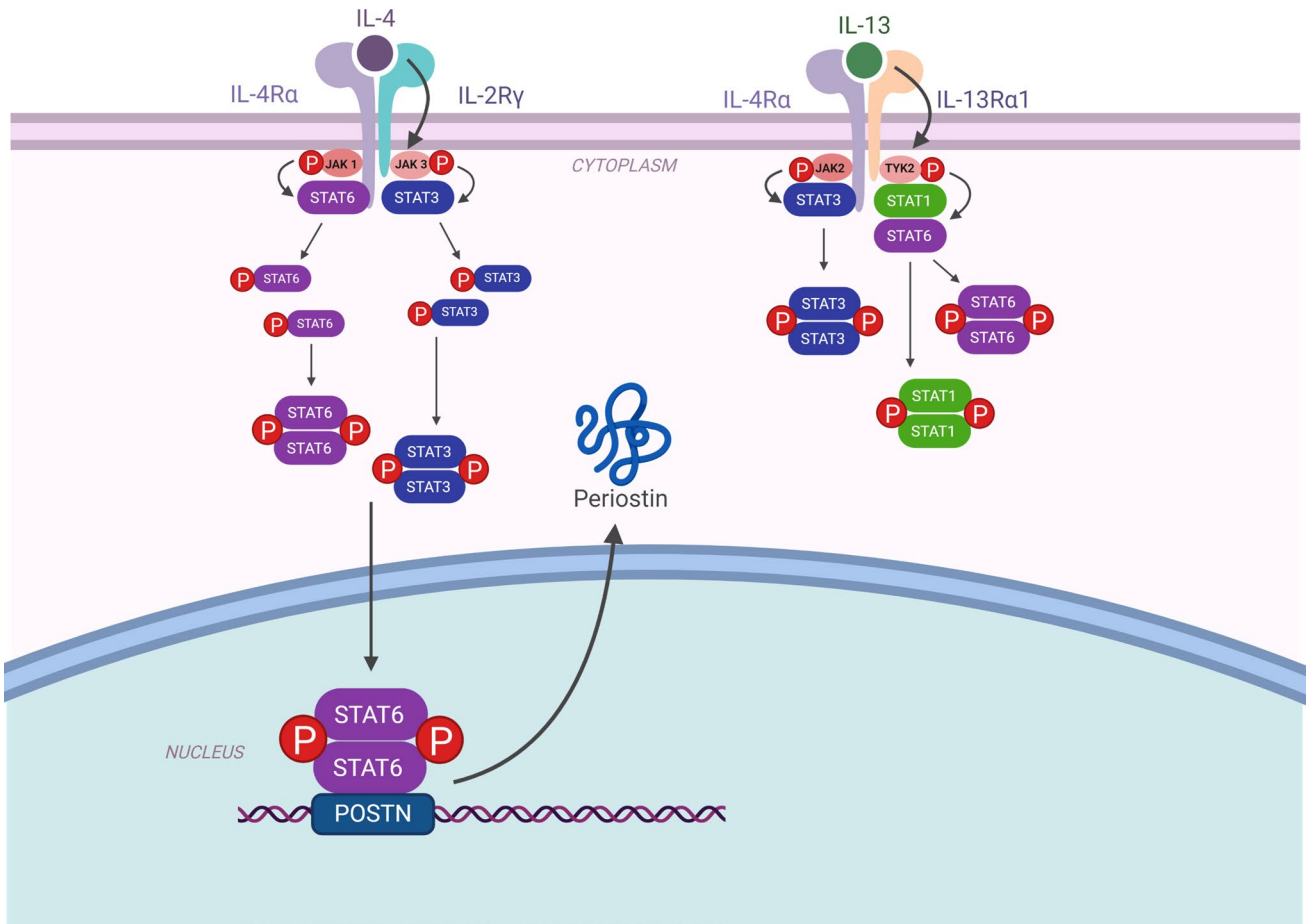

Fig. 1 IL-4 and IL-13 signaling pathways via JAK-STAT signaling cascade. Created with biorender.com. *IL* interleukin, *JAK* Janus kinase, *TYK2* tyrosine kinase 2, *STAT* signal transducer and activator of transcription

and activator of transcription 6 (STAT6) and signal transducer and activator of transcription 3 (STAT3) [11].

Many proteins essential for skin-barrier function—including filaggrin, loricrin, involucrin, and ceramides—are downregulated or inhibited in this way through the effect of IL-4 and IL-13 on gene expression [4]. Additionally, activation of STAT6 results in increased gene expression of periostin, a pro-inflammatory extracellular matrix protein, trophic to keratinocytes that stimulates them to produce TSLP [1]. T_H2 cells also express IL-31, which acts on keratinocytes to potentiate the release IL-24. This, in turn, leads to decreased FLG production and resultant skin barrier breakdown [1, 4].

3 Agents Targeting Interleukin-13 or Its Receptors

IL-13 is a suitable therapeutic target in the treatment of AD, as increased levels of IL-13 correlate well with disease severity [1, 11, 12]. Preventing IL-13 signaling is the basis for three monoclonal antibody treatments for refractory AD—dupilumab, tralokinumab, and lebrikizumab.

3.1 Dupilumab

Dupilumab binds to IL-4Rα, a component of both the IL-4 and IL-13 receptors essential for pro-inflammatory signal transduction [1, 11]. Additionally, by inhibiting activation of the IL-4Rα on sensory nerves, the sensation of pruritus is decreased [1]. In comparison with systemic immunosuppressants like methotrexate and cyclosporine, dupilumab is dosed more conveniently (two initial injections and then one injection every 2 weeks) and provides more targeted immunomodulation.

Several clinical trials support dupilumab's clinical success in treating moderate-to-severe AD (Table 1). In the phase III SOLO-1 randomized controlled trial (RCT), an investigator global assessment (IGA) score of 0 or 1 plus ≥ 2-point improvement from baseline was considered success. By week 16, a larger percentage of patients receiving dupilumab achieved success compared with the group receiving placebo (Table 1) [13]. Additionally, a higher proportion of patients receiving dupilumab achieved Eczema Area and Severity Index (EASI)-75 compared with the group receiving placebo. These results were replicated in the phase III SOLO-2 trial and the phase III LIBERTY AD CAFE trial (Table 1) [13, 14].

In the 76-week open-label long-term extension study, 88.4% of subjects achieved an EASI-75 compared with the baseline of the parent study and 58.0% of subjects achieved a 2-point or greater improvement in IGA score compared with baseline [15]. In a phase III RCT in adolescents, by week 16, a larger percentage of the group receiving dupilumab (either every 2 weeks [41.5%] or every 4 weeks [38.1%]) achieved an EASI-75 when compared with the group receiving placebo (8.2%; $p < 0.001$ for both) [16]. Additionally, by week 16, a larger percentage of the group receiving dupilumab (either every 2 weeks [24.4%] or every 4 weeks [17.9%]) achieved an IGA of 0 or 1 compared with the group receiving placebo (2.4%; $p < 0.001$ for both) [16].

Dupilumab had an acceptable safety profile in clinical trials, which has borne out in clinical practice [17]. Idiopathic and allergic conjunctivitis can occur with dupilumab use, although this side effect is rarely treatment limiting [13, 18, 19]. In the long-term open-label extension study of dupilumab, 18% of the group receiving 2 mg per kg of dupilumab and 16% of the group receiving 4 mg per kg of dupilumab reported conjunctivitis [20]. Conjunctivitis is less likely to occur with dupilumab treatment in other T_H2-driven diseases such as asthma [21]. Additionally, there are several case reports of the development of alopecia areata (AA) after starting dupilumab [22–24]. However, patients with AD have higher rates of AA, and clinical trials found no increased risk in the groups receiving dupilumab compared with placebo [25]. Mouse models of IL-4Rα deletions indicate increased vulnerability to helminthic infections. This is attributed to the necessity of this subunit in dendritic cell maturation. However, an increase in parasitic infections has not been reported in humans using dupilumab [11].

Understanding the clinical effectiveness of dupilumab will impact the reception of the novel agents discussed in later sections. While the trial data presented here may suggest that dupilumab is only modestly effective in moderate-to-severe AD, this underestimates dupilumab's ability to achieve clinically meaningful improvement. The primary outcome measures used in clinical trials (e.g., IGA 0/1 or EASI-75) are investigator-reported measures of disease clearance. However, investigator-reported outcomes do not correlate strongly with patient-reported outcomes, which are key to patients' quality of life—the goal of clinical treatment [26]. Also, while investigator-reported measures of lesion clearance are useful in clinical trials for distinguishing drug from placebo, there is evidence that they underestimate the percentage of patients who have clinically meaningful improvement [27]. This is supported by the results from studies evaluating dupilumab in the real-world setting [17, 28, 29]. Additionally, in clinical practice, when patients have only a partial response to systemic treatment, topical treatment can be added to achieve more complete clearing.

3.2 Tralokinumab

Tralokinumab is a humanized monoclonal IgG_4 antibody (MAB) that neutralizes IL-13 [12]. In a phase IIb RCT, by week 12, there was a larger mean decrease from baseline in

Table 1 Efficacy and safety of published phase II and III clinical trials

Study	Efficacy				Concomitant corticosteroids	Safety
	IGA 0/1 plus ≥ 2-point improvement from baseline	EASI-75	IGA 0/1	Other primary outcome measure		
IL-4Rα antagonists						
Dupilumab						
Adult phase III: SOLO-1 [13]	At week 16[a]: 38%[b] (q2w) and 37%[b] (q1w) improved vs placebo (10%)	At week 16: 51%[b] (q2w) and 52%[b] (q1w) improved vs placebo (15%)			TCS[d] and systemic CS[d]	↑ rate of idiopathic and allergic conjunctivitis in treatment groups vs placebo, ↑ in eosinophils in dupilumab group that resolved by week 16, worsening AD = only serious AE reported in 2 + subjects
Adult phase III: SOLO-2 [13]	At week 16[a]: 36%[b] (q2w) and 36%[b] (q1w) improved vs placebo (8%)	At week 16: 44%[b] (q2w) and 48%[b] (q1w) improved vs placebo (12%)				
Phase III open-label extension in adults [15]	At week 76: 58.0% of subjects improved from baseline of the parent study[c]	At week 76: 88.4% of subjects improved from baseline of the parent study[c]		*Incidence and rate of adverse events* At week 76[a]: there were 420.4 total AEs per 100 patient-years and 8.5 serious AEs per 100 patient-years	TCS	Most common TEAEs: upper respiratory infection, worsening AD, nasopharyngitis, and headache; serious AEs occurred in 7 subjects: lymphoma, prostate cancer, colitis, eczema herpeticum, serum sickness, herpes ophthalmic, worsening AD, and seizure
Adult phase III: LIBERTY AD CAFÉ [14]	At week 16: 39.1%[b] (q1w) and 40.2%[b] (q2w) improved vs placebo (13.9%)	At week 16[a]: 59.1%[b] (q1w) and 62.6%[b] (q2w) improved vs placebo (29.6%)			Medium potency TCS (weeks 2–16) and systemic CS[d]	No serious TEAEs attributed to dupilumab, ↑ rate of conjunctivitis and injection reaction in treatment group vs placebo
Adolescent phase III [16]	At week 16[a]: 24.4%[b] (q2w) and 17.9%[b] (q4w) improved vs placebo (2.4%)	At week 16[a]: 41.5%[b] (q2w) and 38.1%[b] (q4w) improved vs placebo (8.2%)			TCS[d] and systemic CS[d]	Incidence of infections and TEAEs similar across treatment groups; ↑ rate of conjunctivitis and injection-site reactions in groups receiving dupilumab
IL-13 antagonists						
Tralokinumab						
Adult phase IIb [12]	At week 12[a]: no difference at week 12 ($p = 0.10$)	At week 12: 42.5%[b] (300 mg) improved vs placebo (15.5%)		*EASI change from baseline* At week 12[a]: larger mean ↓ from baseline EASI score in treatment groups (150 mg vs 300 mg)[b] vs placebo	TCS	Most common TEAEs: headache and infection of upper respiratory tract, 1 subject developed anti-drug antibodies
Lebrikizumab						
Adult phase II: TREBLE [32]		At week 12: 54.9%[b] (125 mg) improved vs placebo (34.0%)	At week 12: no difference ($p = 0.098$)	*EASI-50* At week 12[a]: 82.4%[b] (125 mg) improved vs placebo (62.3%)	TCS (2 × daily)	No life-threatening TEAEs, no dose-dependent trend in TEAEs

Table 1 (continued)

Study	Efficacy				Concomitant corticosteroids	Safety
	IGA 0/1 plus ≥ 2-point improvement from baseline	EASI-75	IGA 0/1	Other primary outcome measure		
Adult phase IIb [33]		At week 16: 60.6%[b] (250 mg q2w) and 56.1%[b] (250 mg q4w) improved vs placebo (24.3%)	At week 16: 44.6%[b] (250 mg q2w) and 33.7%[b] (250 mg q4w) improved vs placebo (15.3%)	*Least-square mean % change in baseline EASI* At week 16[a]: −72.1%[b] (250 mg q2w) and −69.2%[b] (250 mg q4w) had a mean decrease vs placebo (−41.1%)	TCS[d]	No serious TEAEs were attributed to the drug
IL-31 antagonists						
Nemolizumab						
Adult phase IIb [35]		At week 24: 45.6%[b] (30 mg) improved vs placebo (26.3%)	At week 24: numerically higher, not statistically different ($p = 0.06$)	*Least-square mean % EASI change in from baseline EASI* At week 24[a]: larger mean decrease from baseline EASI score in the treatment group (−68.8%)[b] vs placebo (−52.1%)	TCS	Dose-dependent ↑ in asthma exacerbations in treatment group, 2 study discontinuations due to elevations in CPK
Adult phase II [34]	At week 12: 23.9% (2 mg/kg q4w), 31.4% (0.5 mg/kg q4w), 19.0% (0.1 mg/kg q4w)[c] improved vs placebo (11.9%)	At week 12: 22.3% (2 mg/kg q4w), 37.7% (0.5 mg/kg q4w), 32.3% (0.1 mg/kg q4w)[c] improved vs placebo (18.3%)		*Least-square mean % improvement from baseline pruritus VAS* At week 12[a]: larger mean decrease in pruritus VAS from baseline −63.1%[b] (2 mg q4w), −59.8% (0.5 mg q4w)[b], and −43.7% (0.1 mg q4w) vs placebo (−20.9%)	TCS[d]	Similar number of AEs among the treatment groups and placebo group; serious AEs included retinal detachment ($n = 1$), pyoderma ($n = 1$), worsening AD ($n = 2$), skin infection ($n = 1$), lymphadenopathy ($n = 1$), herpes zoster ($n = 1$), dermatitis exfoliativa ($n = 1$)
Phase II extension in adults [37]	At week 64: 47% (2 mg/kg q8w), 66% (2 mg/kg q4w), 64% (0.5 mg/kg q4w), 58% (0.1 mg/kg q4w)[c] improved from baseline of parent study		At week 64: 32% (2 mg/kg q8w), 38% (2 mg/kg q4w), 32% (0.5 mg/kg q4w), and 35% (0.1 mg/kg q4w)[c] improved from baseline of parent study	*Least-square mean % improvement from baseline pruritus VAS* At week 64[a]: −79.1% (2 mg/kg q8w), −74.7% (2 mg/kg q4w), −89.6% (0.5 mg/kg q4w), and −73.0% (0.1 mg/kg q4w)[c] experienced a mean decrease from baseline of parent study	TCS	No severe AEs; most AEs were mild: headache, lower extremity edema, ↑ CPK, nasopharyngitis, and upper respiratory tract infections

Table 1 (continued)

Study	Efficacy				Concomitant corticosteroids	Safety
	IGA 0/1 plus ≥ 2-point improvement from baseline	EASI-75	IGA 0/1	Other primary outcome measure		
Anti-OX40 antibody						
GBR830						
Adult phase IIa [38]		At day 71: 42.3%[c] (10 mg/kg IV) improved vs placebo (25.0%)	At day 71: 23.1%[c] (10 mg/kg IV) improved vs placebo (12.5%)	*Change from baseline epidermal hyperplasia* At day 71[a]: treatment group had reduced epidermal hyperplasia vs their baseline while placebo group did not[b]	Not stated	Most common TEAEs: headache (16%), atopic dermatitis (13%), and nasopharyngitits (10%)
JAK1 and JAK2 inhibitor						
Baricitinib						
Adult phase III: BREEZE-AD1 [40]		At week 16: 24.8%[b] (4 mg), 18.7%[b] (2 mg), 17.3%[b] (1 mg) improved vs placebo (8.8%)	At week 16[a]: 16.8%[b] (4 mg), 11.4%[b] (2 mg), 11.8%[b] (1 mg) improved vs placebo (4.8%)		TCS[d] and systemic CS[d]	Frequency of TEAEs similar in the placebo vs treatment groups; In BREEZE-AD1 herpes simplex occurred at a higher frequency in the treatment group; ↑ CPK caused treatment interruption for 2 subjects and discontinuation for 1
Adult phase III: BREEZE-AD2 [40]		At week 16: 21.1%[b] (4 mg), 17.9%[b] (2 mg), 12.8%[b] (1 mg) improved vs placebo (6.1%)	At week 16[a]: 13.8%[b] (4 mg), 10.6%[b](2 mg), 8.8%[b](1 mg) improved vs placebo (4.5%)			
Phase II [39]	At week 4: higher % of subjects improved (4 mg) vs placebo ($p = 0.019$), no difference at all other times	At week 16: no difference (2 mg; $p = 0.319$ vs 4 mg; $p = 0.148$)		*EASI-50* At week 16[a]: a higher proportion of treatment subjects (4 mg)[b] improved vs placebo	TCS	↑ CPK, ↓ neutrophil levels, and ↑ platelet levels in the treatment groups but not the placebo group
JAK1 inhibitor						
Upadacitinib						
Adult phase IIb [44]		At week 16: higher % of subjects improved (7.5, 15, or 30 mg)[b] vs placebo	At week 16: higher % of subjects improved (7.5, 15, or 30 mg)[b] vs placebo	*Mean % improvement from baseline EASI* At week 16[a]: 39% (7.5 mg)[b], 62% (15 mg)[b], and 74% (30 mg)[b] improved vs placebo (23%)	None	2 serious TEAEs included 1 jaw pericoronitis, 1 AD worsening, no dose-dependent TEAEs

Table 1 (continued)

Study	Efficacy				Concomitant corticosteroids	Safety
	IGA 0/1 plus ≥ 2-point improvement from baseline	EASI-75	IGA 0/1	Other primary outcome measure		
JAK1 inhibitor						
Abrocitinib						
Phase IIb [41]	At week 12[a]: 43.8%[b] (200 mg) and 29.6%[b] (100 mg) of patients improved vs placebo (5.8%)	At week 12: a higher % of subjects in the treatment groups (200 mg vs 100 mg)[b] improved vs placebo			None	Serious TEAEs in treatment groups: pneumonia ($n=1$), eczema herpeticum ($n=1$), and recurrent herpes simplex ($n=2$); dose-dependent thrombocytopenia seen in doses < 10 mg, these normalized by week 12

AD atopic dermatitis, *AEs* adverse events, *CPK* creatine phosphokinase levels, *CS* corticosteroids, *EASI* Eczema Area and Severity Index, *IGA* investigator global assessment, *IV* intravenous, *qxw* every *x* weeks, *TCS* topical corticosteroids, *TEAEs* treatment-emergent adverse events, ↑ indicate increase, ↓ indicates decrease

[a]Primary endpoint

[b]Statistical significance of at least $p < 0.05$

[c]*p* Value not provided

[d]Allowed for rescue treatment at the investigator's discretion

EASI score in the groups receiving tralokinumab (150 mg vs 300 mg) compared with placebo ($p=0.03$ and $p=0.01$, respectively) [12]. Additionally, by week 12, a higher proportion of subjects achieved an EASI-75 in the group receiving 300 mg of tralokinumab (42.5%) compared with placebo (15.5%; $p=0.003$). However, there was no difference in the percentage of subjects achieving an IGA of 0 or 1 at 12 weeks in the pooled group of subjects receiving tralokinumab ($p=0.10$). Recently, Leo Pharma announced positive preliminary results from the three phase III ECZema TRAlokinumab (ECZTRA 1–3) trials, although this data is not yet publicly available [30]. In a phase I study evaluating the safety of tralokinumab, headache and somnolence occurred in the treatment group but not in the placebo group [31]. In the phase IIb trial, the most common treatment-emergent adverse events (TEAEs) reported were headache and infection of the upper respiratory tract. Only one participant (of 153) developed a positive titer for anti-drug antibodies [12].

3.3 Lebrikizumab

Lebrikizumab is a MAB that binds IL-13, inhibiting the dimerization of IL-13Rα1 and IL-4Rα [32]. One ongoing phase III clinical trial is evaluating lebrikizumab in adults with AD (Table 2). In the phase II TREBLE trial, at 12 weeks, a higher proportion of subjects in the group receiving lebrikizumab 125 mg every 4 weeks achieved an EASI-50 (82.4%) compared with the group receiving placebo (62.3%; $p=0.026$) [32]. Additionally, at 12 weeks, a higher proportion of subjects in the group receiving lebrikizumab 125 mg every 4 weeks achieved an EASI-75 (54.9%) compared with the group receiving placebo (34.0%; $p=0.036$). There was no significant difference in the percentage of subjects achieving an IGA of 0 or 1 between the group receiving lebrikizumab 125 mg every 4 weeks (33.3%) and the group receiving placebo (18.9%; $p=0.098$). A second phase IIb trial in adults reported similar efficacy results (Table 1) [33]. In the TREBLE study, there were no life-threatening adverse events and no adverse events showed a dose-dependent trend [32].

4 Agent Targeting Interleukin 31

4.1 Nemolizumab

Nemolizumab (CIM331) is a MAB that binds the IL-31 receptor α component. This prevents IL-31 from acting on neurons, which inhibits the potentiation of the sensation of pruritus [34–36]. Several phase III clinical trials are ongoing for nemolizumab in AD patients (Table 2). In a 12-week phase II RCT with a 64-week extension, by 12 weeks there

was a mean decrease in pruritus visual analog scale (VAS) from baseline in the group receiving nemolizumab 2.0 mg every 4 weeks (−63.1%) compared with placebo (−20.9%; $p<0.001$) [34]. By 64 weeks, improvement in pruritus VAS compared with baseline was sustained for subjects receiving 0.1 mg/kg every 4 weeks, 0.5 mg/kg every 4 weeks, 2.0 mg/kg every 4 weeks, and 2.0 mg/kg every 8 weeks [37]. By 64 weeks, 68%, 68%, and 66% of subjects receiving nemolizumab 0.1, 0.5, and 2.0 mg/kg every 4 weeks, respectively, achieved an EASI-75 and 74% of subjects receiving 2.0 mg/kg every 8 weeks achieved an EASI-75 [37]. In a phase IIb RCT, by week 24, a higher proportion of subjects achieved an IGA of 0 or 1 in the group receiving nemolizumab 30 mg (36.8%) compared with the group receiving placebo (21.1%; $p=0.06$). By week 24, a larger percentage of subjects in the group receiving nemolizumab 30 mg achieved an EASI-75 (45.6%) compared with the placebo group (26.3%; $p=0.034$) [35].

In the phase I trial, infections were the most commonly reported TEAE. Nasopharyngitis (3 of 27 subjects) and herpes simplex (2 of 27 subjects) were reported in the treatment group but not the placebo group. There were no dose-dependent adverse events [36]. In the long-term extension of a 12-week phase II trial, no severe adverse events occurred for up to 64 weeks after treatment with nemolizumab. Most adverse events were mild and included headache, lower extremity edema, increased creatine phosphokinase levels (CPK), nasopharyngitis, and upper respiratory tract infections [37]. A phase IIb clinical trial reported a dose-dependent increase in mild asthma exacerbations in subjects treated with nemolizumab. Two subjects discontinued the study due to elevations in creatine kinase levels [35].

5 Agent Targeting OX40 (CD134)

5.1 Anti-OX40 Antibody

Anti-OX40 antibody (also called GBR 830) is a humanized monoclonal IgG_1 antibody targeting the costimulatory molecule OX40 (CD134) [38]. OX40 is expressed on activated antigen presenting cells and endothelium and is essential for T-cell expansion [38]. A phase IIb clinical trial is currently recruiting (Table 2). In the published phase IIa clinical trial conducted in adults, the primary study endpoints included incidence and characterization of adverse events, change in epidermal hyperplasia compared with baseline, and mRNA expression signatures from skin biopsy [38]. The treatment group had reduced epidermal hyperplasia (compared with their baseline) at 29 days ($p<0.01$) and 71 days ($p<0.001$) while the placebo group did not. IL-31, CCL11, CCL17, and thymic stromal lymphopoietin (TSLP) levels were all decreased in the treatment group compared with baseline by 71 days ($p<0.001$). IL-4, IL-13, IL-17a, and IL-22 levels were not altered after treatment with GBR830. By day 71, in an intention-to-treat analysis, there was a larger proportion of subjects in the group receiving 10 mg/kg of IV GBR 830 (42.3%) that achieved

Table 2 Ongoing clinical trials (as of April 10, 2020)

Drug	Clinical trial[a]	Phase	Status
Lebrikizumab	NCT04146363	III	Suspended (due to COVID-19)
Nemolizumab	NCT03989206	III	Recruiting
	NCT03985943	III	Recruiting
	NCT03989349	III	Recruiting
Anti-OX40 antibody	NCT03568162	IIb	Recruiting
Baricitinib	NCT03435081 (BREEZE-AD5)	III	Active, not recruiting
	NCT03733301 (BREEZE-AD7)	III	Completed
	NCT03559270 (BREEZE-AD6)	III	Enrolling by invitation
	NCT03334435	III	Active, not recruiting
	NCT03428100	III	Active, not recruiting
	NCT03952559	III	Recruiting
Abrocitinib	NCT03422822	III	Recruiting
Upadacitinib	NCT03607422	III	Recruiting
	NCT03569293	III	Recruiting
	NCT03738397	III	Recruiting
	NCT03568318	III	Recruiting
	NCT03661138	III	Active, not recruiting

[a]ClinicalTrials.gov identifier (www.clinicaltrials.gov)

an EASI-75 compared with the group receiving placebo (25.0%; *p* value was not reported). By day 71, there was a larger proportion of subjects in the group receiving 10 mg/kg of IV GBR 830 (23.1%) that achieved an IGA score of 0 or 1 compared with the group receiving placebo (12.5%; *p* value was not reported). The most common TEAEs were headache (16%), AD (13%), and nasopharyngitis (10%). Adverse events of moderate severity included one subject with facial edema in the placebo group, one subject with a dental abscess, and one subject with worsening AD in the treatment group [38].

6 Agents Targeting the Janus Kinase Family of Proteins

Several small-molecule JAK inhibitors are being actively investigated in the treatment of moderate to severe AD, including baricitinib, abrocitinib, and upadacitinib. The JAK proteins are intracellular and, when activated, activate STAT proteins to dimerize and translocate to the cell nucleus to increase gene expression of inflammatory mediators [8]. Some of the following agents are selective for particular JAK proteins while others inhibit the whole family.

6.1 Baricitinib

Baricitinib is an oral, small-molecule, selective inhibitor of JAK1 and JAK2 [39]. There are ongoing phase III clinical trials (Table 2). In two phase III clinical trials, BREEZE-AD1 and BREEZE-AD2, by 16 weeks, a higher proportion of subjects in the treatment groups (1 mg, 2 mg, and 4 mg) achieved an IGA of 0 or 1, a $\geq$ 2-point improvement, and EASI-75 compared with the group receiving placebo (Table 1) [40]. In a phase II clinical trial in adults with AD, by week 16, a higher percentage of subjects receiving baricitinib 4 mg with a topical corticosteroid (TCS) achieved an EASI-50 than subjects given placebo with TCS ($p=0.027$) [39]. In contrast, by week 16, there was no difference in the proportion of subjects achieving EASI-75 in the group receiving baricitinib (2 mg [$n=20$]; 4 mg [$n=30$]) and TCS compared with the group receiving placebo and TCS ($n=34$; $p=0.319$ and $p=0.148$, respectively). At 4 weeks, a higher proportion of subjects achieved IGA of 0 or 1 after receiving 4 mg of drug and TCS compared with placebo ($p=0.019$). At all other time points, there was no difference in the proportion of treatment subjects achieving IGA of 0 or 1 compared with placebo. No life-threatening adverse events were reported in this study. One serious TEAE was reported (a benign colonic polyp) in one subject receiving baricitinib 4 mg plus TCS. Several adverse events present in the treatment groups but not the placebo group include increased CPK levels, decreased neutrophil levels, and increased platelet levels. In the BREEZE-AD1 and 2 studies, the frequency of TEAEs was similar among the placebo and the treatment groups. In BREEZE-AD1, there was an increased rate of herpes simplex infections in the treatment groups compared with the placebo group but this was not seen in BREEZE-AD2. Elevations in CPK caused treatment suspension in two subjects receiving baricitinib and discontinuation in one subject.

6.2 Abrocitinib

Abrocitinib (PF-04965842) is an oral, small-molecule, selective inhibitor of JAK1 [41]. The recently released data from the phase III trial evaluating abrocitinib monotherapy in subjects 12 years and older, JADE COMPARE, is promising. By 12 weeks, a significantly higher proportion of subjects in the treatment groups (100 mg or 200 mg daily) achieved an IGA of 0 or 1 and a $\geq$ 2-point improvement than the group receiving placebo. The proportion of subjects achieving an EASI-75 was also significantly higher in the treatment groups than the placebo group at 12 weeks [42]. In a phase IIb trial evaluating abrocitinib in moderate-to-severe AD by week 12, a higher proportion of subjects receiving 200 mg of drug and 100 mg of drug (43.8% and 29.6%) had an IGA of 0 or 1 plus a $\geq$ 2-point improvement from baseline compared with those receiving placebo (5.8%; $p<0.001$ and $p<0.001$, respectively) [41]. Additionally, by week 12, a higher proportion of subjects receiving 200 mg of drug and 100 mg of drug (64.6% and 40.7%) obtained an EASI-75 compared with placebo (15.4%; $p<0.001$ and $p=0.004$, respectively) [41]. Four serious TEAEs were reported in the treatment groups, including one case of pneumonia, one case of eczema herpeticum, and two cases of recurrence of herpes simplex. Gastrointestinal upset was also seen with slightly increased frequency in the group(s) receiving abrocitinib. Dose-dependent thrombocytopenia was also noted for doses > 10 mg, but this reversed by week 12 of treatment.

6.3 Upadacitinib

Upadacitinib is an oral small-molecule selective inhibitor of JAK1 [43]. Several phase III clinical trials evaluating upadacitinib in subjects with AD are ongoing (Table 2). In a phase IIb RCT in adults with AD, by week 16, a higher percentage of subjects receiving upadacitinib (7.5, 15, or 30 mg) achieved an EASI-75 than the group receiving placebo ($p \leq 0.001$, $p \leq 0.001$, $p \leq 0.05$, respectively) [44]. Additionally, by week 16, a higher proportion of subjects receiving upadacitinib (7.5, 15, or 30 mg) achieved an IGA of 1 or 0 than the group receiving placebo ($p \leq 0.001$,

$p \leq 0.001$, $p \leq 0.05$, respectively). Of note, this study is the first to evaluate selective JAK1 inhibition in AD patients without concomitant corticosteroid use. Only two serious TEAEs were reported in the treatment group, including jaw pericoronitis in a subject with a history of dental infections and worsening AD in another subject [44]. There were no dose-dependent adverse events. In a phase III RCT comparing upadacitinib and adalimumab in patients with severe rheumatoid arthritis, upadacitinib was generally well tolerated. However, the incidence of herpes zoster infection and elevations in CPK was higher in the group receiving upadacitinib [43].

7 Conclusions

Until recently, the treatment of moderate-to-severe AD relied on potent corticosteroids and systemic immunosuppressants, which can produce significant undesirable side effects. As moderate-to-severe AD can lead to poor quality of life, the development of targeted, well-tolerated immunomodulators remains important. An improved understanding of AD pathophysiology resulted in an explosion of research into new agents for this patient population. While the novel agents discussed here have demonstrated efficacy, others such as tezepelumab, apremilast, ustekinumab, and tradipitant failed to reach their primary endpoint in clinical trials [17, 28, 45, 46].

As new agents come to market, the tradeoff between efficacy and safety will be important. While the JAK inhibitors are effective in clinical trials and offer a much desired oral form of delivery, they are associated with a risk of serious adverse effects [47, 48]. There is an FDA mandated black box warning for risk of severe infection and death when using baricitinib 2 mg in patients with rheumatoid arthritis [48]. This potential for serious adverse events is not surprising, as JAK inhibitors participate in signaling cascades that regulate both the acute inflammatory reaction and hematopoiesis [49, 50].

Leveraging the inhibition of specific subtypes of JAK proteins—only using selective JAK1 inhibitors (upadacitinib) in AD—may help minimize undesired side effects [50]. However, the higher dosages likely required for the treatment of autoimmune disease may overcome the selectivity of these agents at lower dosages [50]. Agents with a wide scope of action may carry a greater risk of serious adverse events compared with agents with a narrow scope of action, such as single interleukin inhibitors [4, 50]. Currently, dupilumab is the only immunomodulator approved in the United States for moderate-to-severe AD, but this may change as several novel agents are successful in clinical trials. It may appear from dupilumab's performance in clinical trials that it insufficiently treats a large sub-group of patients with moderate-to-severe AD. However, the clinical landscape that these novel agents are entering may be different than anticipated, as dupilumab's meaningful clinical performance may be higher than might be expected [17]. Regardless, the benefit of developing several immunomodulators targeting distinct immune pathways is an increased probability of achieving disease control in all AD patients. Additional novel therapies are currently under investigation in clinical trials (APD334, KY1005, bermekimab, and many others). Future research will determine how these novel agents compare directly and if specific immunomodulators work better for certain subtypes of AD patients.

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