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REVIEW

A Narrative Review of the OX40-OX40L Pathway as a Potential Therapeutic Target in Atopic Dermatitis: Focus on Rocatinlimab and Amlitelimab

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ABSTRACT

Atopic dermatitis (AD) is a common chronic inflammatory skin disease involving complex immune dysregulation, including the OX40-OX40L pathway. Rocatinlimab and amlitelimab, monoclonal antibodies targeting OX40 and OX40L, respectively, have shown promise in treating moderate-to-severe AD. Both therapies have demonstrated significant efficacy in reducing disease severity, with favorable safety profiles and no serious treatment-related adverse events. Both treatments outperformed placebo across key clinical endpoints, including skin clearance and symptom reduction, highlighting their potential as effective AD therapies. Although initial results are promising, further research is needed to evaluate the long-term effects, durability of response, and safety of these treatments. These findings support the therapeutic potential of targeting the OX40-OX40L pathway in AD, providing new options for patients with moderate-to-severe disease, with ongoing trials necessary to confirm their sustained benefits.

Keywords: OX40; OX40-OX40L; Rocatinlimab; Amlitelimab; Atopic dermatitis

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Key Summary Points

The OX40-OX40L pathway plays a critical role in both acute and chronic inflammation in atopic dermatitis (AD) by amplifying immune responses across multiple T-cell subsets (Th2, Th1, Th17, and Th22).

Targeting the OX40-OX40L pathway with biologic agents such as rocatinlimab and amlitelimab offers a promising therapeutic approach, reducing both immediate inflammation and long-term disease activity in moderate-to-severe AD.

Rocatinlimab and amlitelimab have demonstrated significant improvements in disease severity, reducing EASI scores and providing sustained clinical benefits after treatment cessation.

Both rocatinlimab and amlitelimab have generally favorable safety profiles, with mild and manageable adverse effects, making them viable options for long-term AD management.

Targeting multiple immune pathways through the OX40-OX40L axis could provide a more comprehensive and individualized treatment strategy for diverse patient populations affected by AD.

INTRODUCTION

Atopic dermatitis (AD) is one of the most common inflammatory skin disorders and the leading cause of nonfatal disease burden among skin conditions globally [1]. About 40% of adults experience moderate-to-severe forms of this chronic condition, which is marked by its variable phenotypic expression and a fluctuating disease course throughout life [2].

The pathogenesis of AD involves different immune responses at various disease stages. Acute lesions are primarily driven by T helper (Th) 2 and Th22 cytokines, acting as central mediators. In contrast, chronic lesions involve additional inflammatory pathways, including those mediated by Th1 and Th17 cytokines. While robust Th2 activation is a hallmark of AD, the contribution of other immune pathways might differ by ethnicity and age. This variability highlights the need for novel therapies targeting multiple immune pathways, particularly for underrepresented populations [3]. Current treatments for moderate-to-severe AD include biologics targeting Th2 cytokines and Janus kinase (JAK) inhibitors, which offer broader, multi-pathway effects. However, a significant unmet need remains for therapies tailored to the diverse mechanisms driving AD inflammation.

The OX40L, expressed on antigen-presenting cells (APCs) and binding to OX40 on activated T cells, plays a pivotal role in driving both acute and chronic inflammatory processes in AD [3–6]. Recent studies have shown that targeting the OX40-OX40L signaling pathway clinically improves AD with an acceptable safety profile [3–5]. These results suggest that this pathway may be a promising therapeutic target for the treatment of moderate-to-severe AD.

This narrative review will explore the OX40-OX40L pathway as a therapeutic target in AD, with a focus on two OX40-OX40L pathway inhibitors: rocatinlimab and amlitelimab. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

AD PATHOGENESIS AND THE ROLE OF THE OX40-OX40L PATHWAY

In AD, the OX40-OX40L co-stimulatory immune checkpoint molecule pair plays a crucial role in immune system regulation. These molecules, part of the tumor necrosis factor superfamily (TNFSF)/tumor necrosis factor receptor superfamily (TNFRSF), are key regulators of adaptive immune responses. OX40 (TNFRSF4, CD134), a co-stimulatory T-cell receptor, and its ligand, OX40L (TNFSF4, CD252), expressed on APCs, are pivotal in AD pathogenesis [4, 7].

Unlike OX40, traditional T-cell activation by naïve T-cells depends on interactions with

co-stimulatory molecules such as CD80/CD86 and CD28 on APCs [8]. However, the OX40-OX40L interaction is critical in amplifying and sustaining the expansion of activated effector Th1 and Th2 T-cells. While resting memory T-cells do not express OX40, upon reactivation, they transform into effector memory T-cells. This OX40 expression, when engaged with OX40L, further drives the expansion of these effector memory cells, perpetuating the inflammatory response in AD [9].

This co-stimulatory pathway contributes to the inflammatory circuit in AD. Thymic stromal lymphopoietin (TSLP) and IL-25 induce OX40L expression on DCs, which in turn promote differentiation of OX40-positive T cells, including Th2 cells. These Th2 cells are central to allergic inflammation, releasing key cytokines such as IL-4 and IL-13 [10]. Additionally, barrier dysfunction in epithelial keratinocytes triggers IL-33 production, which further amplifies the inflammatory cascade by stimulating OX40L expression on type 2 innate lymphoid cells and DCs. Emerging evidence also indicates that OX40-OX40L signaling modulates IL-22 production from T cells, which have been shown to promote keratinocyte proliferation while suppressing filaggrin, thereby perpetuating the cycle of inflammation and barrier dysfunction [3, 8–10].

In patients with AD, both OX40 and OX40L show elevated surface expression on peripheral blood mononuclear cells (PBMCs) compared to healthy individuals. This increased expression is closely correlated with disease activity scores and Th2-associated cytokines, suggesting a potential link between OX40 signaling and the severity of AD inflammation [9, 11].

OX40-OX40L PATHWAY INHIBITORS

Monoclonal antibodies targeting the OX40-OX40L pathway offer a novel approach in the treatment of AD. Rocatinlimab (and telazorlimab, whose development program has been discontinued) targets OX40, modulating the activity of effector and memory T cells. Amlitelimab, an anti-OX40L antibodies, targets antigen-presenting cells, thereby inhibiting the activation of Th2, Th22, and Th17 cytokines in skin lesions.

ROCATINLIMAB

Rocatinlimab (AMG 451) (previously KHK4083) is a novel, human, non-fucosylated monoclonal IgG1 antibody targeting OX40. This mechanism not only decreases the immediate inflammatory response but also has the potential to modify the disease course by preventing the activation and survival of pathogenic T-cells [3].

A multicentre, double-blind, placebo-controlled phase 2b clinical trial was conducted to evaluate the efficacy and safety of rocatinlimab in moderate-to-severe AD unresponsive to topical treatments [3]. The trial included 274 participants, randomly assigned (1:1:1:1:1) to receive double-blind subcutaneous (SC) rocatinlimab or placebo. Specifically, 54 participants received 150 mg every 4 weeks, 54 received 600 mg every 4 weeks, 55 received 300 mg every 2 weeks, and 54 received 600 mg every 2 weeks, while 57 participants were assigned to the placebo group. The treatment groups received rocatinlimab for 36 weeks, followed by a 20-week off-treatment period. In contrast, the placebo group received a placebo for 18 weeks, after which they were switched to 600 mg rocatinlimab SC every 2 weeks, followed by 20 weeks off treatment [3].

Over the 16-week treatment period, rocatinlimab demonstrated significantly greater efficacy compared to placebo in reducing the severity of moderate-to-severe AD. The reduction in EASI scores was substantial across all dosing groups. Patients receiving 150 mg of rocatinlimab every 4 weeks saw a 48.3% reduction in EASI scores, those on 600 mg every 4 weeks experienced a 49.7% reduction, and the groups receiving 300 mg and 600 mg every 2 weeks showed reductions of 61.1% and 57.4%, respectively ($p<0.001$). In contrast, the placebo group achieved only a 15.0% reduction in EASI scores, highlighting the superior efficacy of rocatinlimab [3] (Tables 1,2).

Beyond the primary reduction in EASI scores, secondary endpoint outcomes also favored rocatinlimab over placebo. A higher proportion

Table 1 Main characteristics and results of clinical trials concerning rocatinlimab

Trial	Phase	Study design	Primary endpoint	Main result	Safety
(NCT03703102) [3, 18]	2b	-MC, DB, PC, randomized (1:1:1:1:1), PG in 61 sites in Germany, Japan, Canada, and the US −247 Patients with moderate-to-severe AD participants with EASI score ≥ 16 -Study groups: 150 mg q4w, 600 mg q4w, 300 mg q2w, 600 mg q2w, placebo -Study length: 36 weeks, followed by a 20-week off-treatment period	-The percentage changes in EASI score from baseline to Week 16	Reduction in EASI score: 48.3% for 150 mg q4w; 49.7% for 600 mg q4w; 61.1% for 300 mg q2w; 57.4% for 600 mg q2w; 15% for placebo EASI75 44% for 150 mg q4w; 40% for 600 mg q4w; 54% for 300 mg q2w; 39% for 600 mg q2w; 11% for Placebo EASI90 19% for 150 mg q4w; 12% for 600 mg q4w; 37% for 300 mg q2w; 19% for 600 mg q2w; 4% for Placebo Pruritis NRS score (≥ 4-point reduction) 37% for 150 mg q4w; 46% for 600 mg q4w; 56% for 300 mg q2w; 44% for 600 mg q2w; 19% for placebo −300 mg q2w had the greatest improvement across all endpoints at week 16, which continued through weeks 24 and 36	−175 patients (81%) in the rocatinlimab groups and 41 patients (72%) in the placebo reported adverse events -Most common AE: pyrexia, chills, headache, aphthous ulcers, and nausea -Pyrexia and chills were injection reactions occurred after first dose of rocatinlimab -Incidence of pyrexia was 17% in treatment group vs 4% in placebo -Overall, 9% of patients in the rocatinlimab groups and 21% in placebo discontinued treatment because of AE −1 patient in 150mg q4w had a serious adverse event, an anal abscess, which was attributed to rocatinlimab and led to treatment discontinuation. However, it occurred because of polypectomy and was not considered directly related to treatment -No significant changes in laboratory results, vital signs, or ECG readings

MC multicentre, *DB* double blind, *PC* placebo controlled, *PG* parallel groups, *EASI* Eczema Area and Severity Index, *q4w* every 4 weeks, *q2w* every 2 weeks, *EASI75* 75% reduction in EASI score, *NRS* numerical rating scale, *AE* adverse event, *AD* atopic dermatitis

Table 2 Main characteristics and results of clinical trials concerning amlitelimab

Trial	Phase	Study design	Primary endpoint	Main result	Safety
(NCT03754309) [5, 19]	2a	MC, DB, randomized, PG, in 19 sites in Germany, Poland, Spain, and UK –89 patients with moderate-to-severe AD, participants with ESAI score ≥ 16 -Study groups: low-dose IV (200 mg LD followed by 100 mg maintenance), high-dose IV (500 mg LD followed by 250 mg maintenance), and placebo -Study length: 16 weeks (with 36-week extension study)	-The percentage changes in EASI score from baseline to 16 weeks -Incidence of TEAE	Reduction in EASI score: 80.12% for low-dose group; 69.97% for high-dose group; 49.37% for placebo EASI75: 59% for low-dose group; 52% for high-dose group; 25% for placebo EASI90: 33% for low-dose group; 30% for high-dose group; 13% for placebo vIGA0/1 44% for low-dose group; 37% for high-dose group; 8% for placebo	-TEAE 62% for low-dose group; 47% for high-dose group; 69% for placebo -TEAE included headache, excessive sweating, upper respiratory tract infection, pyrexia, increased aspartate aminotransferase, and iron deficiency anaemia –3 patients experienced severe TEAEs: 2 cases of AD exacerbations in high-dose group and one case of infected dermal cyst in low-dose group (which required surgical intervention but was deemed unrelated to treatment because of the patient's medical history) –2 mild-to-moderate conjunctivitis events (one allergic and one infective) in amlitelimab groups but unrelated to treatment –1 patient in high-dose group experienced insomnia and neck pain but unrelated to treatment –4 patients discontinued the study because of TEAEs: 2 patients in amlitelimab groups discontinued because of AD exacerbations, 1 patient in placebo discontinued because of lack of treatment response, and 1 patient in low-dose group discontinued because of nasopharyngitis -No notable trends were observed in clinical laboratory parameters across any treatment group

Table 2 continued

Trial	Phase	Study design	Primary endpoint	Main result	Safety
(NCT05131477) STREAM AD [12, 20]	2b	-MC, DB, randomized (1:1:1:1:1), PC –390 patients with moderate-to-severe AD -Study groups: 250mg SC q4w with 500mg LD; 250 mg SC q4w; 125mg SC q4w; 62.5mg SC q4w; placebo -Study length: 24 weeks (with 36-week maintenance/withdrawal phase)	-The percentage changes in EASI score from baseline at week 16	IGA 0/1 and/or EASI-75 at 28 weeks: 69.2% for 250 mg SC q4w with 500 mg LD; 58.8% for those in the withdrawal group	-No safety concerns reported

MC multicentre, *DB* double blind, *PG* parallel groups, *LD* loading dose, *TEAE* treatment emergent adverse events, *vIGA0/1* validated Investigator Global Assessment Score of 0 (clear) or 1 (almost clear), *PC* placebo controlled, *AD* atopic dermatitis, *LD* loading dose, *q4w* every 4 weeks, *IV* intravenous, *SC* subcutaneous

of patients in the rocatinlimab groups achieved this significant improvement, with 38.9–53.8% of rocatinlimab-treated patients reaching a 75% reduction in EASI scores (EASI-75) compared to only 10.5% in the placebo group. Moreover, a greater improvement in the pruritus numerical rating scale (NRS) score (≥ 4-point reduction) was observed, with 36.5–55.8% of patients in the rocatinlimab groups achieving this compared to 19.3% in the placebo group. Notably, the 300 mg dose of rocatinlimab administered every 2 weeks demonstrated the greatest improvement across all endpoints at week 16, with this improvement continuing through weeks 24 and 36 [3] (Table 1).

A sub-study analysis was conducted to examine the transcriptomic and proteomic profiles in serum samples and skin biopsy specimens from patients with AD. Specimens were collected at baseline, week 8, week 16, week 36 and week 52 from 20 Japanese patients out of 150. The analysis revealed significant changes, particularly in non-lesional skin. Additionally, quantitative polymerase chain reaction results showed downregulation of genes encoding several T helper cells, including Th2, Th1, Th17, and Th22, along with a reduction in OX40 mRNA expression following treatment with rocatinlimab. These treatment effects persisted from week 36 through week 52, even after treatment cessation. Furthermore, pruritis and the Th2/Th22 ratio were reduced, based on proteomic analysis of serum samples at week 16. A secondary analysis assessed the efficacy of rocatinlimab in the head and neck region using an adjusted EASI score (0.1, adjustment for 10% weighting). The result showed continued improvement compared to placebo up to week 56, 20 weeks after treatment had stopped [4].

In the rocatinlimab groups, adverse events were generally comparable across treatment arms. Throughout the initial 18-week double-blind period, 175 patients (81%) in the rocatinlimab groups and 41 patients (72%) in the placebo group reported adverse events. The most commonly reported adverse events, occurring in ≥ 5% of patients in the rocatinlimab groups and more frequently than in the placebo group, were pyrexia, chills, headache, aphthous ulcers, and nausea. Both pyrexia and chills were

classified as injection reactions by investigators, typically occuring after the first dose of rocatinlimab. These reactions were mild to moderate in severity and did not result in treatment discontinuation. The incidence of pyrexia was 17% in the treatment group compared to 4% in the placebo group, whereas the incidence of serious adverse events ranged from 2 to 6% in the rocatinlimab groups compared to 2% in the placebo group [3]. One patient receiving 150 mg rocatinlimab every 4 weeks experienced a serious adverse event, specifically an anal abscess, which was attributed to the study drug and led to treatment discontinuation. This event occurred after a medical procedure for polyp removal and a diagnosis of early stage rectosigmoid cancer. However, the event was not considered directly related to rocatinlimab treatment as the patient had other risk factors such as smoking and alcohol use. No serious allergic reactions or deaths were reported during the study. Overall, 9% of patients in the rocatinlimab groups and 21% in the placebo group discontinued treatment because of adverse events. There were no significant changes in laboratory results, vital signs, or ECG readings. The safety profile observed throughout the study remained consistent with findings from the initial 18-week period [3].

The ongoing phase 2 and 3 clinical trials for rocatinlimab are listed in Table 3.

AMLITELIMAB

Amlitelimab (KY1005/SAR445229) is a fully human, non-depleting IgG4 anti-OX40L monoclonal antibody that selectively binds to and blocks OX40L. In addition to inhibiting T-cell activation via APCs, amlitelimab also interrupts OX40L back signaling, blocking T cell-independent inflammatory pathways. This dual mechanism offers potential for addressing not only type 2 inflammation but also Th1-, Th17-, and Th22-driven inflammation [5].

In the phase 2a (NCT03754309) double-blind, randomized, controlled trial, 89 patients with moderate-to-severe AD were enrolled. After accounting for one protocol deviation, 88 patients received either low-dose intravenous (IV) amlitelimab ($n=29$), high-dose IV amlitelimab ($n=30$), or placebo ($n=29$). Baseline disease characteristics were generally well matched across treatment groups, although the placebo group had a slightly higher proportion of patients with severe AD based on the validated Investigator Global Assessment (vIGA) score. Patient retention was moderate to high throughout the study. Notably, 67% of patients ($n=59$) completed the primary 16-week study, with higher completion rates in the high- and low-dose amlitelimab groups compared to placebo (69%, 73%, and 59%, respectively). This trend continued into the 36-week extension study, where 57% of patients ($n=50$) completed the study, with completion rates of 59%, 63%, and 48% in the low-dose, high-dose, and placebo groups, respectively [5]. The low-dose consisted of a 200 mg IV loading dose followed by 100 mg IV maintenance, while the high dose included a 500 mg IV loading dose followed by 250 mg IV maintenance. Both doses were administered every 4 weeks [5].

Secondary efficacy endpoints further highlighted the benefits of amlitelimab, with a higher proportion of patients achieving significant clinical improvements. By week 16, 59% of patients in the low-dose group and 52% in the high-dose group achieved EASI-75 compared to only 25% in the placebo group. Additionally, EASI-90 was achieved by 33% of patients in the low-dose group and 30% in the high-dose group, while only 13% in the placebo group reached this level of improvement. Moreover, the proportion of patients with clear or almost clear skin, as reflected by a vIGA score of 0 or 1, was significantly higher in the amlitelimab groups (44% in the low-dose group and 37% in the high-dose group) compared to only 8% in the placebo group ($p<0.001$ for both amlitelimab groups versus placebo) [5] (Table 2).

Amlitelimab demonstrated a generally favorable safety profile. While most patients in all groups reported at least one treatment-emergent adverse event (TEAE) by week 16 (62% in the low-dose amlitelimab group, 47% in the high-dose group, and 69% in the placebo group), certain events, such as headache, excessive sweating, upper respiratory tract infection, pyrexia, increased aspartate aminotransferase (a liver

Table 3 Summary of ongoing phase 2 and 3 clinical trials concerning rocatinlimab in AD

Phase	Trial	Age group	Total study duration (weeks)	Primary endpoint	Status
III	NCT05882877 (ROCKET-ASCEND) [21]	Children/Adolescents/Adults ≥ 12 to ≤ 100 years	116	TEAEs	Recruiting
III	NCT05704738 (ROCKET-ASTRO) [22]	Children/Adolescents ≥ 12 to ≤ 17 years	52	EASI75 at Week 24; vIGA0/1 and ≥ 2-point reduction in IGA at Week 24	Recruiting
III	NCT06224192 (ROCKET-Outpost) [23]	Children/Adolescents/Adults ≥ 12 to ≤ 100 years	12	Successful self-administration of rocatinlimab subcutaneous using devices for injection at home	Recruiting
III	NCT05398445 (ROCKET-Ignite) [24]	Adults ≥ 18 to ≤ 100 years	24	EASI75 at Week 24; vIGA0/1 and ≥ 2-point reduction in IGA at Week 24	Active, not recruiting
III	NCT05633355 (ROCKET-Orbit) [25]	Children/Adolescents ≥ 12 to ≤ 17 years	52	TEAEs	Active, not recruiting
III	NCT05899816 (ROCKET-VOYAGER) [26]	Adults ≥ 18 to ≤ 54 years	24	Effect on vaccine (anti-tetanus and anti-meningococcal) antibody responses	Active, not recruiting
III	NCT05651711 (ROCKET-Horizon) [27]	Adults ≥ 18 to ≤ 100 years	24	EASI75 at Week 24; vIGA0/1 and ≥ 2-point reduction in IGA at Week 24	Completed
III	NCT05724199 (ROCKET-SHUTTLE) [28]	Adults ≥ 18 to ≤ 100 years	24	EASI75 at Week 24; vIGA0/1 and ≥ 2-point reduction in IGA at Week 24	Active, not recruiting

TEAE treatment emergent adverse events, *vIGA0/1* validated Investigator Global Assessment Score of 0 (clear) or 1 (almost clear), *EASI* Eczema Area and Severity Index, *EASI75* 75% reduction in EASI score, *AD* atopic dermatitis

enzyme), and iron deficiency anaemia, were observed slightly more frequently in the amlitelimab groups compared to placebo, with a difference of > 5% for these events [5].

While amlitelimab exhibited a generally favorable safety profile with no treatment-related serious adverse events, three patients experienced severe TEAEs: two cases of AD exacerbations in the high-dose amlitelimab group and one case of an infected dermal cyst in the low-dose group, which required surgical intervention but was deemed unrelated to treatment because of the patient's medical history. Additionally, two mild-to-moderate conjunctivitis events (one allergic and one infective) were reported in the amlitelimab groups, both considered unrelated to treatment and not affecting the patients' ability to complete the study. One patient in the high-dose group also experienced insomnia and neck pain, neither of which was deemed related to the treatment [5].

A total of four patients discontinued the study because of TEAEs. Two patients in the amlitelimab groups discontinued because of exacerbations of their underlying AD, one patient in the placebo group discontinued because of lack of treatment response, and one patient in the low-dose amlitelimab group discontinued because of nasopharyngitis. No notable trends were observed in clinical laboratory parameters across any treatment group, and no specific safety concerns were identified [5].

A phase 2b (NCT05131477) multicentre, randomized, double-blind, placebo-controlled, dose-ranging study was conducted in 390 adults with moderate-to-severe AD. The study included a 24-week treatment phase followed by a 36-week maintenance/withdrawal phase. During the treatment phase, participants were randomized to receive amlitelimab subcutaneously every 4 weeks at varying doses: 250 mg with a 500 mg loading dose, 250 mg without a loading dose, 125 mg, or 62.5 mg, or a placebo for 24 weeks. The primary outcome was the percentage change in EASI score from baseline at week 16 [12].

Amlitelimab treatment resulted in significant improvements in EASI scores across all dosing groups compared to placebo. Patients who continued treatment with amlitelimab maintained high EASI-75 and IGA 0/1 responder rates through 28 weeks [13]. In patients receiving 250 mg every 4 weeks following a 500 mg loading dose, 69.2% maintained a strong response (IGA 0/1 and/or EASI-75) at 28 weeks compared to 58.8% of those in the withdrawal group [13]. Interestingly, high responder rates were also seen in patients who discontinued the treatment [13]. Reductions in biomarkers, such as TARC, eosinophils, and IL-22, persisted even after serum amlitelimab levels became negligible, indicating that OX40L blockade results in prolonged modulation of inflammatory T cells and long-lasting control of AD after amlitelimab withdrawal [13]. Amlitelimab was well tolerated across all dose groups, with no safety concerns reported [12].

The ongoing phase 2 and 3 clinical trials for amlitelimab are listed in Table 4.

DISCUSSION

AD is a common yet complex chronic inflammatory skin disease affecting 13% of children and 7% of adults worldwide, with up to 40% of adults experiencing moderate-to-severe forms of the disease [2, 14]. Despite its prevalence, the underlying pathophysiology remains poorly understood. The primary hypothesis suggests that AD stems from an immune imbalance, particularly in T-cell subsets, with a predominance of Th2 cells producing type 2 cytokines such as IL-4, IL-5, IL-13, and IL-31, leading to elevated IgE production [15].

The OX40-OX40L pathway is a key regulator of immune responses in AD. It also interacts with other immune cells, such as mast cells and type 2 innate lymphoid cells (ILC2), which promotes the inflammatory response in AD [16]. The upregulation of OX40 and OX40L in patients with AD points to the critical role this pathway plays in both local and systemic inflammatory processes [17]. The OX40-OX40L pathway serves an essential role in amplifying inflammation by promoting the release of cytokines, which contribute to hallmark symptoms of AD, including pruritus, disruption of the skin barrier, and persistent inflammation [16]. The activation of

Table 4 Summary of ongoing phase 2 and 3 clinical trials concerning amlitelimab in AD

Phase	Trial	Age group	Total study duration (weeks)	Primary endpoint	Status
II	NCT05769777 (ATLANTIS) [29]	Children/Adolescents/ Adults ≥ 12 years	180	TEAEs, TESAEs	Recruiting
II	NCT05492578 (RIVER-AD) [29]	Adults ≥ 12 years	332	TEAEs	Recruiting
II	NCT06015308 (HYDRO) [30]	Adults ≥ 18 years	36	Effect on vaccine antibody responses	Recruiting
III	NCT06181435 (COAST 2) [31]	Children/adolescents/ adults ≥ 12 years	44	EASI75 at Week 24; vIGA0/1 and ≥ 2-point reduction in IGA at Week 24	Recruiting
III	NCT06130566 (COAST 1) [32]	Children/adolescents/ adults ≥ 12 years	44	EASI75 at Week 24; vIGA0/1 and ≥ 2-point reduction in IGA at Week 24	Recruiting
III	NCT06407934 (ESTUARY) [33]	Children/adolescents/ adults ≥ 12 years	64	EASI75 at Week 48; vIGA0/1 and ≥ 2-point reduction in IGA at Week 48	Recruiting
III	NCT06224348 (SHORE) [34]	Children/adolescents/ adults ≥ 12 years	44	EASI75 at Week 24; vIGA0/1 and ≥ 2-point reduction in IGA at Week 24	Recruiting
III	NCT06241118 (AQUA) [35]	Children/adolescents/ adults ≥ 12 years	56	EASI75 at Week 36; vIGA0/1 and ≥ 2-point reduction in IGA at Week 36	Recruiting

TEAE treatment emergent adverse events, *TESAE* treatment emergent serious adverse events, *vIGA0/1* validated Investigator Global Assessment Score of 0 (clear) or 1 (almost clear), *EASI* Eczema Area and Severity Index, *EASI75* 75% reduction in EASI score, *AD* atopic dermatitis

various immune pathways highlights the necessity for a more comprehensive therapeutic strategy. Thus, the OX40 pathway has emerged as a promising target for treating moderate-to-severe AD, offering the potential to reduce persistent immune responses that drive the chronic and severe nature of the disease [17]. By targeting this mechanism, novel treatment options may be developed to potentially minimize flare-ups and provide long-term improvements, as early clinical studies with OX40-targeting antibodies have shown encouraging results [17].

Amlitelimab and rocatinlimab are novel treatments targeting OX40-OX40L pathway. Clinical trials for both drugs have demonstrated significant improvement in reducing EASI scores as a primary endpoint after 16 weeks of treatment. Amlitelimab is a non-depleting IgG4 anti-OX40L monoclonal antibody, while rocatinlimab is a non-fucosylated monoclonal IgG1 antibody, targeting OX40, a key player in T-cell differentiation and memory induction. Both medications work by selectively binding to and blocking the OX40-OX40L pathway, thereby restoring immune balance by promoting anti-inflammatory T-cell activity and suppressing pro-inflammatory responses [3, 5].

Current evidence suggests that targeting the OX40-OX40L pathway could significantly improve the management of moderate-to-severe AD. Both rocatinlimab and amlitelimab demonstrated substantial efficacy in reducing disease severity, as measured by EASI, with an acceptable safety profile during phase II trials.

Both amlitelimab and rocatinlimab demonstrated generally favorable safety profiles. Mild and manageable pyrexia and chills were the most common adverse events associated with rocatinlimab, which were not seen with amlitelimab.

At this stage, direct comparisons between these two agents would be premature. Nonetheless, both medications demonstrated significant improvement over placebo, highlighting their potential as effective treatments for moderate-to-severe AD. These findings align with the growing evidence that supports the role of the OX40-OX40L axis in AD pathogenesis, particularly in amplifying the Th2-mediated inflammatory response, a hallmark of AD [3, 5].

The efficacy of both amlitelimab and rocatinlimab is in line with other advanced treatments for AD, yet each offers distinct advantages. Given their comparable efficacy and manageable safety profiles, both rocatinlimab and amlitelimab represent promising future options in the management of AD. Future head-to-head trials are necessary for a more definitive comparison.

A notable limitation of this review is the small number of studies and publications on the role of the OX40-OX40L pathway in AD. Further research is necessary to evaluate their long-term effects on AD progression, and ongoing trials will be essential in assessing their long-term safety and durability of response.

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Declarations

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