

# Updated Review on Treatment of Atopic Dermatitis

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## ■ Abstract

Atopic dermatitis (AD) is a chronic or chronically recurrent inflammatory dermatosis associated with multiple triggers that has a complex pathophysiological mechanism. It is characterized by a heterogeneous clinical expression, signs, and symptoms. Its etiology and pathogenesis are complex and are influenced by multiple immune-mediated factors. Treatment of AD can also be complex, given the high number of available drugs and multiple therapeutic targets. In this review, we summarize current literature on the efficacy and safety of topical and systemic drugs to treat moderate-to-severe AD. We begin with topical treatments such as corticosteroids and calcineurin inhibitors and subsequently address the latest systemic treatments, such as Janus kinase inhibitors (upadacitinib, baricitinib, abrocitinib, gusacitinib) and interleukin (IL) inhibitors, which have proven efficacious in AD, namely, dupilumab (IL-4 and IL-13), tralokinumab (IL-13), lebrikizumab (IL-13), and nemolizumab (IL-31). Given the large number of drugs available, we summarize the pivotal clinical trials for each drug, evaluate recent real-world experience in terms of safety and efficacy for purposes of compilation, and provide evidence to guide the optimal choice of therapy.

**Key words:** Atopic dermatitis. JAK inhibitors. Interleukin. Biologics. Dermatology.

## ■ Resumen

La dermatitis atópica (DA) es una dermatosis inflamatoria crónica o crónicamente recurrente, asociada a múltiples desencadenantes y con un mecanismo fisiopatológico complejo. Se caracteriza por una expresión clínica, signos y síntomas heterogéneos. Su etiopatogenia es compleja y está influenciada por múltiples factores inmunomediados. El tratamiento de la DA también resulta complejo; esto se debe a que existen varios fármacos que pueden utilizarse para tratar la DA con múltiples dianas terapéuticas. En esta revisión, resumimos la literatura actual sobre la eficacia y seguridad de los fármacos tópicos y sistémicos para tratar la DA de moderada a grave. Partiremos desde tratamientos tópicos como los corticoides y los inhibidores de la calcineurina tópicos, hasta los últimos tratamientos sistémicos como los inhibidores cinasas Jano JAK (upadacitinib, baricitinib, abrocitinib, gusacitinib) y los inhibidores de la interleucina (IL) que han demostrado eficacia sobre la DA: dupilumab (IL-4 e IL-13), tralokinumab (IL-13), lebrikizumab (IL-13) y nemolizumab (IL-31). Como hemos visto existen multitud de fármacos para tratar la DA, por este motivo hemos realizado una revisión en la cual se han tenido en cuenta todos los ensayos clínicos de fase III de cada fármaco. También ha sido evaluada su experiencia reciente en la práctica clínica en concepto de seguridad y eficacia con el propósito de compilar esta evidencia para ayudar a seleccionar la terapia adecuada.

**Palabras clave:** Dermatitis atópica. Inhibidores de JAK. Interleucina. Biológicos. Dermatología.

## Introduction

Atopic dermatitis (AD) is a chronic or chronically recurrent inflammatory dermatosis with a genetic basis. It is associated with multiple triggers and has a complex pathophysiological mechanism. Clinical expression is very heterogeneous in terms of both age at presentation and signs and symptoms. The defining feature of the disease is the presence of eczema, which is accompanied by intense pruritus and dry skin and reflects alteration of the barrier function and dysfunction of the immune system towards a type 2 helper T cell ( $T_H2$ ) response [1], although other inflammatory pathways may participate in the same way (eg,  $T_H17$ ,  $T_H22$ , or  $T_H1$ ), depending on the age (pediatric) and origin/ethnicity of the patient (Asian/European).

AD is a heterogeneous disease involving environmental agents that can act as triggers in genetically susceptible individuals. For decades, controversy has surrounded whether AD is a disease that is pathogenically conditioned by an alteration in barrier function and that favors an inadequate immune response or, on the contrary, an immune dysfunction that also ends up altering barrier function, the most accepted proposal at present. However, the clinical heterogeneity observed prevents us from ruling out the existence of a different and synergistic role for both triggers in different patient subpopulations and phenotypes. In this sense, AD is currently considered a model of imbalance between  $T_H1$ - and  $T_H2$ -type inflammatory responses, with a predominance of the  $T_H2/T_H22$  response in both acute and chronic forms and with the participation of the  $T_H17$  pathway and a contribution of the  $T_H1$  axis, particularly in its more chronic forms. This proposal is, without doubt, very simplified and will vary significantly, with the contribution of other inflammatory pathways depending on the clinical phenotype [2].

The objective of treatment in AD is to reduce inflammation, maintain the barrier function of the skin, alleviate pruritus, and avoid superinfections caused by the degradation of the stratum corneum [3]. Long-term treatment of AD consists of achieving clinical remission or minimal levels of activity through maintenance therapy, with sufficient flexibility to add specific treatments for disease exacerbations during flare-ups.

## Topical Treatments

Topical treatment of AD to date has relied on the use of topical corticosteroids and topical calcineurin inhibitors (pimecrolimus and tacrolimus), which can be used to treat or prevent disease. Below, we list a series of products that are currently under development.

### Topical Inhibitors of the JAK/STAT Pathway

These drugs are being tested in the treatment of AD following the successful oral administration of agents such as ruxolitinib, which is a JAK1/JAK2 inhibitor, or delgocitinib, a JAK inhibitor. The Table summarizes the drugs currently under development [4-5] and for which evidence from clinical trials is available.

### Topical Inhibitor of Phosphodiesterase-4

Crisaborole 2% is the first approved phosphodiesterase 4 (PDE-4) inhibitor in adults and children older than 2 years with mild-to-moderate AD. Phase 3 data demonstrated efficacy in terms of the Investigator Global Assessment scale (IGA) 0 (51.7%) and IGA-1 (48.5%) compared with vehicle (40.6% and

**Table.** Topical JAK Inhibitors.

Investigational agent	Inhibition target	Acronym	Number of patients, age	Phases	Endpoint	Interventions (arm)	Result
Ruxolitinib	JAK1, 2	TRuE AD1 TRuE AD2	631 ( $\geq 12$ y) 618 ( $\geq 12$ y)	3 3	Wk 8 Wk 8	0.75% Ruxolitinib cream 1.5% Ruxolitinib cream Vehicle	IGA $\geq 2$ improvement response rate: 50.0%/39.0%/15.1% IGA $\geq 2$ improvement response rate: 39.0%/51.3%/7.6%
Tofacitinib	JAK1, 2, 3		69 (18-60 y)	2	Wk 4	2% Tofacitinib ointment Vehicle	EASI change from baseline: 81.7%-29.9%
Ifidancitinib (ATI-502)	JAK1, 3		22 ( $\geq 18$ y)	2	Wk 4	Ifidancitinib topical solution	PGA $\geq 2$ grade improvement from baseline: 41.2% EASI percent change from baseline: 40% SPA percent change from baseline: 31%
Delgocitinib (LEO 124249)	JAK1, 2, 3 and Tyk2		44 ( $\geq 2$ y) 158 ( $\geq 18$ y)	1 3	Wk 8 Wk 4	Delgocitinib cream Delgocitinib 0.5% ointment Vehicle	Not available mEASI change from baseline: -44.3%/1.7%
Brepocitinib (PF-06700841)	JAK1/Tyk 2		292 (12-75 y)	2	Wk 6	Brepocitinib cream Vehicle	Not available

Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; JAK, Janus kinase; PGA, Physician Global Assessment; Tyk, tyrosine kinase.

29.7%, respectively) at 4 weeks, with minor adverse effects, such as pain or burning at the application site [6].

Other PDE-4 inhibitors include difamilast 1% ointment which led to an improvement in IGA 0 or 1 of 20.9% at week 4 [7]. The results of a phase 3 study were recently published [8]. Patients aged 15 to 70 years received difamilast 1% ointment or vehicle twice daily for 4 weeks. The primary endpoint of IGA 0-1 with  $\geq 2$ -grade improvement at week 4 was achieved by 38.46% of patients in the ointment group, compared with 12.64% in the vehicle group. Lotamilast and roflumilast are other, similar PDE-4 inhibitors under study [9-10].

### Aryl Hydrocarbon Receptor Agonists

The aryl hydrocarbon receptor (AhR) is a member of the Per-Arnt-Sim (PAS) superfamily of transcription factors. AhR is broadly expressed in the skin, and, when activated, it upregulates gene expression of filaggrin, loricrin, and involucrin, thus accelerating epidermal terminal differentiation.

Tapinarof is a topical AhR-modulating agent that regulates expression of skin barrier protein, has antioxidant activity, and suppresses IL-17 and IL22 [10]. A randomized, multicenter, phase 2b, double-blind, vehicle-controlled study (NCT02564055) is the most important completed trial for AD to date. In this study, 247 adults and adolescent patients were randomized to receive tapinarof cream (0.5% or 1%) or a vehicle control, either once daily or twice daily for 12 weeks with a 4-week follow-up period. At week 12, IGA response rates (IGA 0 or 1) were 53% (1% twice daily), 46% (1% once daily), 37% (0.5% twice daily), and 34% (0.5% once daily) compared with 24% (vehicle twice daily) and 28% (vehicle once daily). This improvement was maintained for the 4-week follow-up period [11].

### Transient Receptor Potential Vanilloid 1 Antagonists

Transient receptor potential vanilloid 1 (TRPV1) has been shown to play a role in pruritus, epidermal barrier function, and inflammation. TRPV1 is overexpressed in AD lesions, and its activation results in the production of molecules that promote itch and inflammation. Therefore, blocking this protein could have therapeutic potential.

Asivatrep is a potent and selective antagonist of TRPV1 that has been evaluated in a phase 2b study (NCT02757729). The study was conducted on 194 adults (19-70 years) with mild-to-moderate AD. Patients were randomized to asivatrep 0.1%, 0.3%, 1.0%, or vehicle twice daily for 8 weeks. The IGA success rates were 14.6% for vehicle cream, 42.6% for 0.1% cream, 38.3% for 0.3% cream, and 57.5% for 1.0% cream [12].

### Skin Microbiome Modulators

Several strategies are currently under development with the aim of modulating the AD skin microbiota, either by decreasing the *Staphylococcus aureus* population or by increasing the normal microbiota.

Ominagan is an antimicrobial peptide gel that is being investigated as a possible treatment for various infectious and inflammatory disorders. For AD, a phase II trial randomized

36 patients with mild to moderate disease 1:1:1 to ominagan gel 1%, ominagan gel 2.5%, and vehicle, once daily for 4 weeks. Small but significant results in body surface area (BSA), SCORing Atopic Dermatitis (SCORAD), and pruritus were observed only in the 2.5% arm [13].

The niclosamide ATx201 can also achieve decolonization of *S aureus*. In a phase 2 trial (NCT03304470), 31 patients with mild-to-severe AD received ATx201 cream 2% and a matching vehicle once daily for 3 weeks. Treatment was generally safe, and the histological and transcriptional profiling analysis on day 22 demonstrated that treatment significantly increased the expression of biomarkers related to the skin-barrier function and decreased expression levels of markers related to inflammation [14].

### Newer Emollients

Recent years have seen an increase in the number of nonmedicated emollients containing active ingredients termed “emollient plus” or therapeutic moisturizers that improve the skin barrier with antipruritic, anti-inflammatory, and antioxidant effects. The active ingredients include ceramides, saponins, colloidal oatmeal, and nonpathogenic bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis*. In vitro and clinical research data indicate that these drugs may target specific molecules. A prospective, double-blind, placebo-controlled clinical trial demonstrated that patients with mild AD who received cream with 5% *V filiformis* decreased SCORAD levels and pruritus significantly compared with those who received placebo [15].

### JAK Inhibitors

#### Upadacitinib

Upadacitinib is authorized in the European Union (EU) for the treatment of moderate-to-severe AD in adults and adolescents aged  $\geq 12$  years who are candidates for systemic treatment. It is a selective and reversible inhibitor of the JAK1 enzyme and is metabolized mainly by CYP3A4, with the result that its plasma concentrations may be affected by coadministration of strong inhibitors or inducers of CYP3A4. Regarding the pharmacodynamic interactions, combination with cyclosporine or other immunosuppressants should be avoided, as the additive immunosuppressive effect has not been studied [16].

The efficacy and safety of upadacitinib 15 mg and 30 mg in adolescents and adults with AD was evaluated in 3 phase 3 randomized double-blind placebo-controlled 16-week multicenter trials (Measure Up 1, Measure Up 2, and AD Up). The efficacy of upadacitinib was evaluated in monotherapy in the Measure Up 1 and 2 studies and in combination with topical corticosteroids in the AD UP study [17-19]. The proportion of patients who had achieved an Eczema Area and Severity Index (EASI) of 75 at week 16 was significantly higher in the upadacitinib 15 mg group (70%) and upadacitinib 30 mg (80%) groups than in the placebo group (16%) in Measure Up 1. Efficacy at week 16 was maintained through week 52. At week 52, EASI-75 was achieved by 82.0% and 79.1% of patients continuing the 15-mg dose and 84.9% and 84.3% of

patients continuing the 30-mg dose (for Measure Up 1 and Measure Up 2, respectively). A V-IGA score of clear (0) or almost clear (1) with 2 or greater grades of improvement was achieved by 59.2% and 52.6% and 62.5% and 65.1% of patients in the Measure Up 1 and Measure Up 2 studies, respectively. Treatment discontinuation due to adverse events was infrequent overall, although it was slightly more frequent for the upadacitinib 30-mg dose [20].

A recent head-to-head comparative clinical trial comparing upadacitinib and dupilumab [21] found that at week 16, 71% of patients receiving upadacitinib and 61.1% patients receiving dupilumab achieved EASI-75 ( $P=0.006$ ). All ranked secondary endpoints also demonstrated the superiority of upadacitinib over dupilumab at week 16.

Safety data in AD reveal the most common adverse events ( $\geq 1/10$ ) to be infections of the upper respiratory tract (25.4%) and acne (15.1%). Less frequent ( $\geq 1/100$  to  $< 1/10$ ) were herpes simplex (8.4%) and zoster, folliculitis (3.2%), influenza (2.1%), anemia and neutropenia (2.3%), cough (3.2%), headache (6.3%), abdominal pain (2.9%), nausea (2.7%), fever (2.1%), elevated creatine phosphokinase (5.5%), weight gain, urticaria, and fatigue. Other infrequently detected adverse effects ( $\geq 1/1,000$  to  $< 1/100$ ) were bronchitis and pneumonia, oral candidiasis, hypercholesterolemia, hypertriglyceridemia, and elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [18].

Treatment requires analytical monitoring with, for example, the absolute neutrophil and lymphocyte counts and hemoglobin (at least, before starting treatment and 12 weeks later and thereafter according to symptoms), liver transaminases (before starting treatment and thereafter according to clinical practice), and lipids (12 weeks after starting treatment and thereafter, according to guidelines). Treatment should be stopped in cases with an absolute neutrophil count  $< 1 \times 10^9$  cells/L, absolute lymphocyte count  $< 0.5 \times 10^9$  cells/L, hemoglobin  $< 8$  g/dL, or if treatment-induced liver dysfunction is suspected [17].

Several studies have analyzed upadacitinib in clinical practice. Vanlerbergh et al [22] included AD patients from 18 French centers, 54 of whom were treated with the 15-mg dose and 12 with the 30-mg dose. Approximately 75% of the patients had received cyclosporine and dupilumab, and more than half had received at least 3 systemic/biological treatments. Efficacy results were measured at 12 and 24 weeks. In relation to the 15-mg dose, 37.5% of the patients reached the IGA 0-1 proposed as the main measure of efficacy at 6 months, while with the 30-mg dose, this value was reached by 75% ( $n=3$ ). From a safety point of view, the most reported adverse effect was elevated cholesterol and triglyceride levels without thromboembolic effects. As for survival, it is noteworthy that treatment with upadacitinib 15 mg was stopped in at least 9 patients.

Pereyra-Rodriguez et al [23] recently reported on the efficacy and safety results in the short term (16 weeks) and long term (52 weeks). This Spanish multicenter study included 16 hospital centers from all over Spain. In the short-term study, of the 43 patients included, 90.7% had previously received treatment with cyclosporine and 74.4% with dupilumab. Almost two thirds (60.4%) received the 30-mg dose. The

high baseline EASI value (24.9 [9.6]) and impact on quality of life (DLQI 17.4 [6.8]) stood out. At 16 weeks, the mean EASI decreased to 4.1 [4.6] (83.5% improvement;  $P<0.0001$ ), and 62.8% had IGA 0-1 at the end of the follow-up period. Only 1 patient discontinued treatment, in this case for safety reasons. The data at 52 weeks, however, were only obtained in 22 patients of the previously mentioned cohort. In this case, and without reporting efficacy and safety data inconsistent with short-term data, it should be noted that the probability of survival of the drug was 77.3%, with no differences because of dose, sex, or previous treatments.

Hagino et al [24] presents us with a retrospective series of 31 patients with moderate-severe AD. The short-term efficacy evaluation shows a reduction of 85.6% in EASI at 12 weeks and 81.3% in the AD Control Tool (ADCT). Multivariate linear regression analysis revealed that a high percent reduction of EASI at week 4 or 12 was associated with high baseline eosinophil count or female sex. No adverse effects other than those already described in clinical trials were reported.

### Baricitinib

Baricitinib is authorized in the EU for the treatment of moderate-to-severe AD in adults who are candidates for systemic treatment. It has been marketed in 2-mg and 4-mg tablets. The recommended dose is 4 mg once daily orally in general and 2 mg for patients aged  $\geq 75$  years or with a history of chronic or recurrent infections or in cases of pharmacokinetic interactions. In patients with a sustained response who are candidates for baricitinib, the dose can be reduced to 2 mg.

Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2. It is a substrate of CYP3A4 and the transporter of organic anions (OAT3), P-glycoprotein, breast cancer resistance protein, and the multidrug and toxic extrusion protein 2-K. The only known clinically relevant pharmacokinetic interaction was recorded with strong inhibitors of OAT3 such as probenecid. In this case, the recommended dose is 2 mg once daily. Its combination with other immunosuppressive drugs is governed by the same conditions as upadacitinib [25].

The efficacy and safety of baricitinib administered in monotherapy or in combination with topical corticosteroids was evaluated in 3 phase 3 randomized double blinded placebo-controlled 16-week studies (BREEZE-AD1, -AD2, and -AD7) [26-27]. At the start of the BREEZE-AD7 study, all patients were receiving concomitant treatment with topical corticosteroids and were allowed to use topical calcineurin inhibitors.

As for the pivotal monotherapy-based clinical trials, in BREEZE-AD1, more patients achieved the primary endpoint of V-IGA for AD (0-1) with baricitinib 4 mg and 2 mg at week 16 than with placebo (16.8% with 4 mg and 11.4% with 2 mg). In BREEZE-AD2, the results were 13.8% for baricitinib 4 mg and 10.6% for 2 mg. Itch began to improve as early as week 1 for 4 mg and week 2 for 2 mg. The most common adverse events in patients treated with baricitinib were nasopharyngitis and headache. These results improved with the combination of topical corticosteroids expressed in BREEZE-AD7, with 23.9% of patients reaching V-IGA 0-1 with the 2-mg dose and 30.6% with the 4-mg dose.

The BREEZE-AD3 [28] study is a long-term extension study with data available up to 68 weeks of cumulative treatment for BREEZE-AD1 and BREEZE-AD2 patients and up to 32 weeks for BREEZE-AD7 patients. A sustained response was generally observed in patients with at least some response (IGA 0, 1, or 2) after initiating baricitinib.

Two short series report data from real-world clinical practice. Uchiyama et al [29] present a series of 14 patients who had completed the 12-week treatment without interruption in a single center. All patients received baricitinib 4 mg. The EASI response analysis revealed that 100% of the cases reached EASI-50 (14/14), 64.2% EASI-75 (9/14), and 35.7% EASI-90 (5/14) at week 12. In this retrospective study, EASI-75 at week 12 was more frequent (63%) than in clinical trials. Rogner et al [30] also present a series of 12 patients with moderate-severe AD whose efficacy and safety were evaluated at 12 weeks. EASI-75 (as a measure of efficacy) was reached by 90.1% of patients. Curiously, the evaluation of pruritus, quality of life, and insomnia was more favorable in patients who had not received treatment with dupilumab. The previously mentioned French cohort [20] included 34 patients treated with baricitinib 4 mg. In relation to the primary endpoint, 41.2% of the patients reached IGA 0-1. Baricitinib was stopped in 8 patients, mainly owing to lack of efficacy.

### Abrocitinib

Abrocitinib is a JAK-1 inhibitor indicated for the treatment of moderate-to-severe AD in adults who are candidates for systemic treatment. The recommended starting dose is 200 mg once daily, although an initial dose of 100 mg once daily is recommended for patients aged  $\geq 65$  years. Abrocitinib can be used with or without topical drug treatments for AD, although the same standard as the rest of the molecules in its class must be applied with respect to the simultaneous use of immunosuppressants [31]. Treatment discontinuation should be considered in patients who show no signs of improvement after 24 weeks.

In the phase 3 clinical trials MONO-1 and MONO-2 [32], 62.7% and 61% of patients reached EASI-75 in monotherapy after 12 weeks of treatment with the 200-mg dose. These results improved with the addition of topical corticosteroids (70.3%). The percentage of patients who reached EASI-75 with the 100-mg dose did not reach 60% in either of the 2 scenarios, namely, with and without topical corticosteroids. Recent data from a head-to-head clinical trial with dupilumab [33] showed that a larger proportion of patients treated with abrocitinib reached the primary outcomes, namely, PP-NRS4 at week 2 and EASI-90 at week 4.

### Gusacitinib

Gusacitinib (Asana BioSciences) is a dual inhibitor of the JAK and SYK pathways that is being tested orally. In a phase 2b trial with 36 patients, EASI-50 and NRS pruritus were achieved in almost all cases after 4 weeks of treatment with doses of 20, 40, and 80 mg. An EASI-75 response was achieved in 63% of patients treated with 40 mg and 50% of patients treated with 80 mg every 24 hours, compared with 22% in the placebo group [34]. The improvement in the EASI was

correlated with a decrease in the skin  $T_H2$  and  $T_H22$  biomarkers. The results of a placebo-controlled phase 2b trial to evaluate the efficacy and safety of ASN002 in moderate-to-severe AD (220 patients) are pending (NCT03531957) [35].

## Biologic Therapies

### Dupilumab

Dupilumab is authorized in the EU for the treatment of moderate-to-severe AD in adults and adolescents aged  $\geq 12$  years who are candidates for systemic treatment. The recommended starting dose is 600 mg SC at week 0, followed by a dose of 300 mg every 2 weeks. Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signaling. Dupilumab inhibits IL-4 signaling through the type I receptor (IL-4R $\alpha$ / $\gamma$ c) and IL-4 and IL-13 signaling through the type II receptor (IL-4R $\alpha$ /IL-13R $\alpha$ ) [36].

The efficacy and safety profile of dupilumab in monotherapy and in combination with topical corticosteroids of moderate potency has been evaluated in 3 randomized, double-blind, placebo-controlled clinical trials (LIBERTY AD SOLO-1, LIBERTY AD SOLO-2, and LIBERTY AD CHRONOS) [37-38]. The results demonstrate the superiority of dupilumab, both in monotherapy and in combination with topical treatment, with significant differences compared to placebo in the percentage of patients with improvement in EASI-75 at 16 weeks of the order of 32%-37% in monotherapy and 46% in combination with topical treatment. A reduction in EASI was observed with respect to the baseline measurement of 84.9% at 52 weeks. Improvements in pruritus were observed compared to placebo (25% vs 30%) on the NRS scale. Significant differences with respect to placebo were also observed in quality of life (Dermatology Life Quality Index), symptoms of depression and anxiety (Hospital Anxiety and Depression Scale), and symptoms reported by the patient (Patient Oriented Eczema Measure scale) [39].

The efficacy of dupilumab in patients with severe AD and inadequate response to cyclosporine, intolerance, or absence of a medical indication was confirmed by the results of a 32-week randomized, double-blind, placebo-controlled phase 3 clinical trial. At week 16, differences of 33% were observed in the proportion of patients with improvement in the EASI-75 compared to placebo, ie, similar to those observed in the pivotal trials. Improvements in pruritus of the order of 28.5% compared to placebo were observed on the NRS scale [40].

Responders in the SOLO-1 and SOLO-2 trials were randomized to receive placebo, dupilumab weekly or every 2 weeks, dupilumab every 4 weeks, or dupilumab every 8 weeks for an additional 36 weeks (LIBERTY AD SOLO-CONTINUE study). A favorable effect on EASI was observed in patients randomized to the weekly/2-weekly regimens; in more spaced regimens, the effect was smaller and more antidrug antibodies developed [41].

The safety analysis showed that the main adverse events were injection site reactions, and infections (conjunctivitis, blepharitis, nasopharyngitis, upper respiratory tract infections, sinusitis, and oral herpes). The incidence of conjunctivitis

ranged from 3.0% to 6.4% and, in general, the symptom was mild or moderate in intensity and self-limiting. Some authors recommend the use of artificial tears when starting treatment with dupilumab [42].

Since dupilumab was authorized for use in AD in adults, several real-world evidence studies have been conducted [43-47]. One systematic review and meta-analysis of real-world evidence for dupilumab analyzed 22 studies and 3303 AD patients. The pooled proportion of patients achieving a 50%, 75%, and 90% improvement in EASI was 85.1%, 59.8%, and 26.8%, respectively. Conjunctivitis was the most common adverse event, reported in a pooled proportion of 26.1% (8.10%) [48].

### *Tralokinumab*

Tralokinumab is authorized in the EU for the treatment of moderate-to-severe AD in adults who are candidates for systemic treatment. The recommended starting dose is 600 mg SC in week 0, followed by doses of 300 mg every 2 weeks. Tralokinumab is a fully human IgG4 monoclonal antibody that binds with high affinity to interleukin 13 (IL-13) and inhibits its interaction with IL-13 receptors. It neutralizes the biological activity of IL-13 by blocking its interaction with the IL13R $\alpha$ 1/IL-4R $\alpha$  receptor, which greatly decreases type 2 (T<sub>H</sub>2) inflammatory mediators [49-50].

The efficacy and safety of tralokinumab both as monotherapy and in combination with topical corticosteroids (TCS) was evaluated in 3 pivotal randomized double-blind, placebo-controlled trials (ECZTRA 1, ECZTRA 2, and ECZTRA 3) [50-51]. Tralokinumab 300 mg every 2 weeks in monotherapy (ECZTRA 1 and ECZTRA 2) proved superior to placebo in terms of patients who achieve an IGA response of 0-1, an EASI-75, and/or a  $\geq$ 4-point improvement in NRS daily worst itch through week 16. The proportion of patients achieving IGA 0-1 or EASI-75 up to week 52 was 56.2% when tralokinumab 300 mg monotherapy every 2 weeks was used and 50% when tralokinumab 300 mg was administered every 4 weeks. A percentage of nonresponders at week 16 benefited from continued treatment, and response was achieved in 20% (IGA 0-1) and 40% (EASI-75) at week 52.

When tralokinumab was combined with TCS (ECZTRA 3) [52], tralokinumab 300 mg every 2 weeks + TCS was superior to placebo + TCS in IGA 0-1, EASI-75, and/or  $\geq$ 4-point improvement in daily most severe pruritus according to NRS. Additionally, tralokinumab 300 mg every 2 weeks enabled a 50% reduction in the use of topical corticosteroids compared with the placebo group. Both as monotherapy and in combination with TCS, tralokinumab improved patient-reported symptoms (measured using the POEM scale) and the impact of AD on sleep quality (as measured using the eczema-related sleep NRS) at week 16.

Tralokinumab (300 mg any dosage) was well tolerated both as monotherapy and in combination with TCS. The observed adverse effects in ECZTRA 3 were consistent in both the short and the medium term. The most frequent adverse reactions were mild or moderate in nature, including upper respiratory tract infections, mainly reported as the common cold, injection site reactions, conjunctivitis, and allergic conjunctivitis. Unadjusted comparisons suggest a lower risk of conjunctivitis with specific IL-13 inhibition than with dual

IL-4/IL-13 (dupilumab) inhibition [53], although the evidence is not robust. In both treatments, concomitant use of artificial tears and an ophthalmological examination is recommended in cases of conjunctivitis that do not resolve with standard treatment.

The efficacy and safety profile of tralokinumab was also analyzed in combination with TCS in adults with moderate-to-severe AD and an inadequate response or intolerance to cyclosporine A (ECZTRA 7) [54]. An EASI-50 response of 80% and an EASI-75 response of 64.2% were observed in the experimental group at week 16.

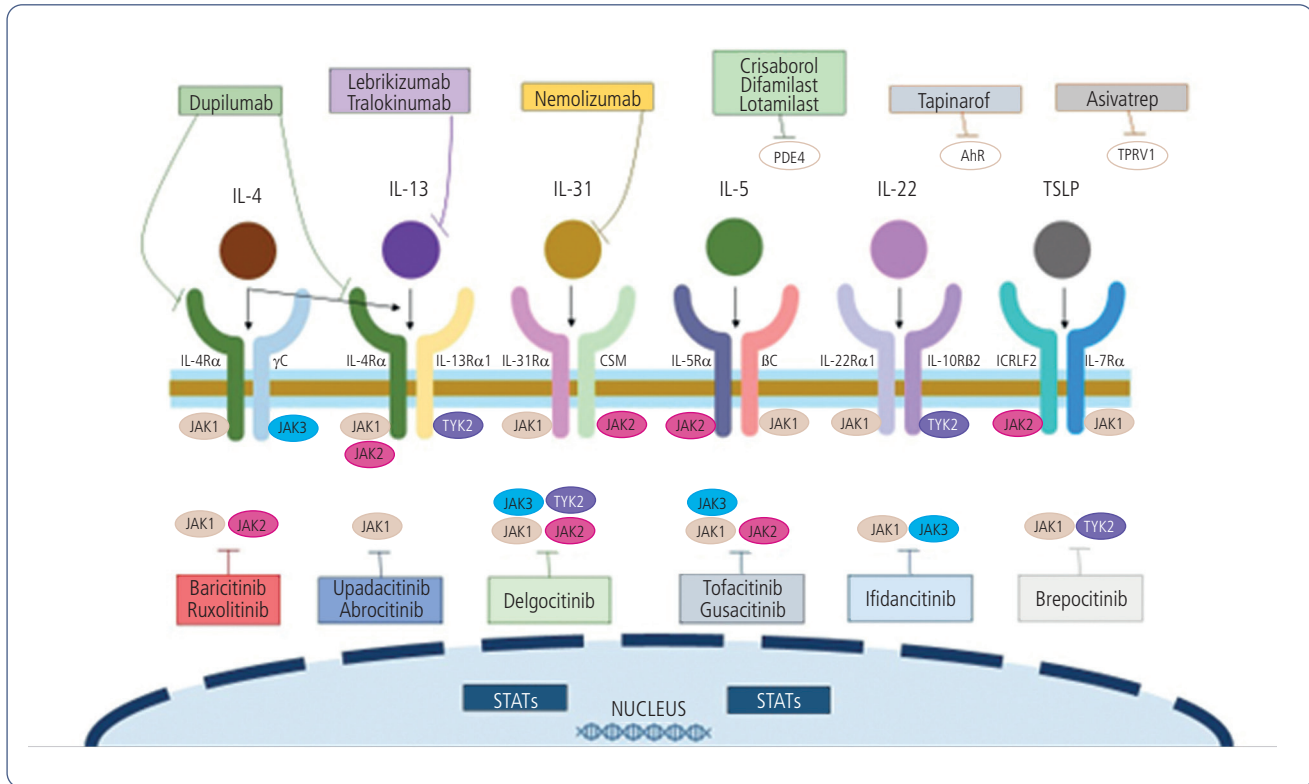
No real-world evidence for tralokinumab has been published to date.

### *Lebrikizumab*

Lebrikizumab is a subcutaneous drug that functions as an IL-13 inhibitor [55]. It is a fully human IgG4 $\kappa$  monoclonal antibody that binds specifically to soluble IL-13 in an epitope (<10 pM) that overlaps with the IL-4R $\alpha$  binding site, avoiding signalling through the IL-4R $\alpha$ /IL-13R $\alpha$ 1 heterodimeric receptor. Lebrikizumab does not prevent IL-13 from binding to IL-13R $\alpha$ 2, thus favoring this endogenous mechanism of regulation [56].

A phase 2b double-blind placebo-controlled randomized clinical trial evaluated lebrikizumab in patients with moderate-to-severe AD up to 16 weeks in 280 patients. At the end of the study, the lebrikizumab-treated groups showed a dose-dependent statistically significant improvement in the primary endpoint compared with placebo: 125 mg every 4 weeks (-62.3%), 250 mg every 4 weeks (-69.2%), and 250 mg every 2 weeks (-72.1%). A significant impact on pruritus (differences with placebo-treated patients for  $\geq$ 4-point improvement in NRS) was seen as early as day 2 in the high-dose lebrikizumab group. Treatment-emergent adverse events, mostly mild-to-moderate, were reported in 57%-61.3% of lebrikizumab patients (vs 46.2% in placebo patients). Low rates were reported for injection-site reactions (1.9% in the placebo group vs 5.7% in all lebrikizumab groups). Herpesvirus infections (3.8% vs 3.5%) and conjunctivitis (0% vs 2.6%) were also reported [57].

ADvocate1 (ADv1, NCT04146363) and ADvocate2 (ADv2, NCT04178967) are identically designed phase 3 trials evaluating the efficacy and safety of lebrikizumab monotherapy in adolescent and adult patients with moderate-to-severe AD [58]. At the end of week 16, IGA 0-1 was achieved by 43.1% and 33.2% (ADv1 and ADv2) compared with 10.8%-12.7% in the placebo group, EASI-75 in 58.8% and 52.1% vs 16.2%-18.1%, and  $>$ 4-point improvement in pruritus NRS in 45.9% and 39.8% compared with 11.5%-13% in the placebo group, respectively. For those patients who responded to lebrikizumab 250 mg every 2 weeks at the end of the 16-week induction period, more patients treated with lebrikizumab every 2 weeks (75.5% and 64.6% in Adv 1 and 2, respectively) and lebrikizumab every 4 weeks (74.2% and 80.6%) maintained an IGA of 0-1 with a  $\geq$ 2-point improvement than those in the lebrikizumab withdrawal arm (46.5% and 49.8%). EASI-75 was maintained by 79.2% and 77.4% of patients treated with lebrikizumab every 2 weeks and 79.2% and 84.7% treated with lebrikizumab every 4 weeks compared with 61.3% and 72% in the placebo groups. In ADv1 and ADv2, 81.2% and 90.3% of



**Figure.** Mechanism of action of the new treatments for atopic dermatitis. IL indicates interleukin; PDE, phosphodiesterase; AhR, aryl hydrocarbon receptor; TRPV, transient receptor potential vanilloid; JAK, Janus kinase; STAT, signal transducer and activator of transcription protein.

patients taking lebrikizumab every 2 weeks maintained a  $\geq 4$ -point improvement from baseline to week 52 on the Pruritus NRS compared with 80.4% and 88.1% of patients on lebrikizumab every 4 weeks, respectively. The percentage of patients in the lebrikizumab withdrawal arm who maintained a Pruritus NRS response was 65.4% (ADv1) and 67.6% (ADv2). Across treatment arms, the percentage of patients using any rescue therapy was 14.0% (ADv1) and 16.4% (ADv2). Interestingly, dosing with lebrikizumab every 4 weeks from week 16 up to week 52 provided a similar clinical response to lebrikizumab every 2 weeks. Loss of clinical response following withdrawal of lebrikizumab was slow, with approximately half of the patients re-randomized to placebo still showing a response at week 52.

The safety profile of lebrikizumab is consistent with previously published data over 16 weeks. Conjunctivitis was detected in 8.1%-8.3% in patients taking lebrikizumab at 52 weeks. Loss of clinical response following withdrawal of lebrikizumab was slow, with approximately half of the patients re-randomized to placebo still showing a response at week 52 [58].

### Nemolizumab

Nemolizumab is a monoclonal antibody that targets the  $\alpha$  receptor of the neuroimmune cytokine interleukin 31 (IL-31) [59].

A phase 2b study compared the effect of nemolizumab (10, 30, and 90 mg) every 4 weeks together with topical corticosteroids in adults with moderate-to-severe AD, severe pruritus, and inadequate control with topical treatment

(TCS) for 24 weeks. Nemolizumab (30 mg) reduced EASI scores compared with placebo at week 24 ( $-68.8\%$  vs  $-52.1\%$ ). Significant differences were observed at week 8, with improvement after 1 week. IGA 0-1 was higher for nemolizumab 30 mg than placebo at week 16 but not at week 24; this was attributed to an increased placebo/TCS effect (36.8% vs 21.1%). Pruritus NRS scores were improved for nemolizumab 30 mg compared with placebo at week 16 and week 24, with a difference observed by week 1. NRS response rates ( $>4$ -point decrease) were greater for nemolizumab 30 mg than for placebo at week 16 and week 24. Most patients resorted to medium-potency TCS, although placebo-treated participants used almost twice the amount of the nemolizumab group. Nemolizumab was well tolerated at all doses, with few serious or severe adverse events. In patients with a history of asthma, a greater incidence of asthma events was observed with nemolizumab in a dose-dependent fashion. All asthma events were mostly mild in severity, and there were no de novo cases of asthma associated with nemolizumab [60].

Kabashima et al [61] published the results from 2 phase 3, multicenter long-term studies of nemolizumab for the treatment of pruritus associated with AD in Japanese patients (JP01 and JP02) whose disease was inadequately controlled with topical agents and oral antihistamines. In this study, nemolizumab 60 mg every 4 weeks was administered subcutaneously alongside topical treatments. Study JP01 patients received double-blind nemolizumab or placebo for 16 weeks and then entered a 52-week extension period in which all patients received nemolizumab (nemolizumab/nemolizumab and

placebo/nemolizumab groups). In study JP02, patients received nemolizumab for 52 weeks. In the nemolizumab/nemolizumab group, there were clinically meaningful improvements from the start of treatment to week 68 in the pruritus visual analog scale (66% decrease) and EASI (78% decrease). The long-term safety profile was consistent with that reported in Silverberg et al [60].

In a meta-analysis of randomized clinical trials, Xiao et al [62] evaluated a total of 4 randomized trials of nemolizumab (1 phase 1 trial, 2 phase 2 trials, and 1 phase 3 trial). In a total of 729 patients recruited, treatment with nemolizumab led to significantly decreased EASI scores compared with the placebo group (standardized mean difference [SMD] of  $-0.31$ ) and the VAS for pruritus (SMD of  $-3.95$ ). The adverse event rate did not differ significantly between the placebo control and nemolizumab groups or between the 4 trials. In a response letter to this meta-analysis, Freemantle and Piketty [63] claimed that by using different statistical evaluations, they observed a numerically greater benefit for the 30-mg dose every 4 weeks, which is under evaluation in 2 pivotal phase 3 trials (NCT03989349 and NCT03985943). In a more recent meta-regression analysis of randomized controlled trials, Liang et al [64] described a reduction of  $-18.86$  in the pruritus VAS (weighted mean difference) and of  $-11.76$  EASI in a total of 14 cohorts of participants from 6 randomized controlled studies. No significant difference was observed in the occurrence of any adverse event compared with the placebo groups.

Nemolizumab is being evaluated in 2 identical phase 3 pivotal studies (Arcadia 1 and 2) and a long-term extension study, which aim to recruit 1500 patients [64,65].

## Conclusions

We reviewed the therapeutic alternatives that we have incorporated into the treatment of AD (Figure). The efficacy and safety results were excellent for all of them. However, AD is a highly heterogeneous syndrome, for which it is generally not advisable to prioritize specific drugs. Consequently, therapy must be tailored according to the clinical characteristics of the patient, efficacy and safety profile, speed of action, risk of tumorigenesis, desire to become pregnant, comorbidities, and drug interactions. Registries with large patient populations and real-world evidence studies are necessary to generate scientific evidence on the efficacy and safety profile of these new treatments.

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### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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