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Review

Recent Advances in Treating Atopic Dermatitis

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A B S T R A C T

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin condition and the leading cause of the global burden from skin disease. The etiology of AD is multifactorial, including genetic predisposition, skin barrier dysfunction, immunological dysregulation caused by T-helper cell imbalances, environmental factors (allergens, pollutants and climate) and stress.

Diagnosis of AD is based on clinical criteria, which are supplemented by allergen testing and, in certain circumstances, skin biopsies. Treatment of AD is individual and should be tailored to the respective patient. Beside basic therapy (emollients and avoidance of allergens), current therapeutic options include topical and systemic corticosteroids, calcineurin inhibitors, biologics (dupilumab, tralokinumab, lebrikizumab and recently approved nemolizumab), Janus kinase (JAK)inhibitors (baricitinib, abrocitinib, upadacitinib), phototherapy and psychosomatic counselling. The current European and US-American guidelines on the management of AD adhere to a stepwise treatment approach, starting with topical therapies and extending to systemic therapies in moderate to severe cases. Novel topical therapies such as JAK inhibitors (ruxolitinib, delgocitinib), phosphodiesterase 4 (PDE4) inhibitors (crisaborole, difamilast, roflumilast) and the aryl hydrocarbon receptor agonist tapinarof have recently been approved in the US and Japan.

This review presents the most recent advances in understanding and treating atopic dermatitis. A special focus is given to recent developments within the AD drug pipeline. The most advanced new drug developments are the monoclonal antibody amlitelimab targeting the OX40/OX40L pathway and the oral TYK2 inhibitor ICP-332 for systemic administration. Novel topical therapies include ointments of pan-JAK inhibitors MH004, CGB-500 and LNK01004 and the antimicrobial gel zabalafin.

Keywords: Atopic dermatitis, Biologics, PDE4 inhibitors, JAK inhibitors, Novel drugs

1. Introduction

Atopic dermatitis (AD) is s a chronic, recurrent inflammatory skin condition and the leading cause of the global burden from skin disease. Chronic recurrent eczema, severe itching, dry and sensitive skin, often beginning in early childhood, as well as a family or personal history of atopy (asthma, hay fever) are important characteristics of AD. Typical distribution patterns of AD lesions are depending on age. In infants (i), eczema lesions are often more acute than in adults and mainly located on the face and the extensor surfaces of the limbs. The trunk might be affected but the nappy area is typically spared. From age 1-2 years and onwards (ii), polymorphous manifestations with different types of skin lesions are seen, particularly in flexural folds. In adolescents and adults (iii), often lichenified

and excoriated plaques are found, particularly at flexures, wrists, ankles and eyelids; in the head-and-neck type, the upper trunk, shoulders and scalp are involved. Adults might have only chronic hand eczema or they might present with prurigo-like lesions[1]. Clinical manifestations include acute flare-ups with erythematous, exudative lesions, chronic phases with lichenification, hyperkeratosis; often accompanied by agonising itching (pruritus), which can severely impair sleep and quality of life. Atypical vascular reactions, keratosis pilaris, ichthyosis and periorbital changes can facilitate diagnosis. Other chronic dermatological diseases with similar phenotypes such as psoriasis, seborrheic eczema, contact dermatitis, ichthyosis, scabies, cutaneous lymphomas need to be excluded to assure correct AD diagnosis.

The prevalence of AD varies significantly between geographic regions, age and sex groups (more frequent in children and women) and diagnostic criteria. Epidemiological studies from 1992 to 2022 showed that around 101.27 million adults and 102.78 million children worldwide have AD, corresponding to prevalence rates of 2.0% (95% UI 1.4–2.6) and 4.0% (95% UI 2.8–5.3), respectively[2]. The prevalence of AD is rising worldwide. A recent survey conducted by a polling company between January and April 2023, targeted individuals aged 16 years or older in 20 countries across five continents, demonstrated that AD now affects nearly 10% of individuals of 16 years and over. The highest prevalence was observed in Asia (e.g., South Korea 15.3% and China 15.1%) followed by Europe (e.g., Spain 13.1%) and Latin America (e.g., Mexico 10.7%), with North America (e.g., USA 7.3%) and Africa (e.g., 7.2%) showing the lowest rates. AD was significantly more common in female patients across all regions, a finding that is consistent with previous studies[3].

The etiology of AD is multifactorial, including genetic predisposition (e.g., filaggrin mutations), skin barrier dysfunction, immunological overreaction, environmental factors (allergens, pollutants) and stress. In addition, the Western life-style (increased hygiene standards including the inadequate use of antimicrobials and a diet poor in fibres and rich in saturated fats and carbohydrate sweeteners) may reduce the skin and gut microbiome especially during early childhood and as a consequence reduce the activation of regulatory dendritic cells and regulatory T cells (Tregs) resulting in a prevalent stimulation of T helper 2 (TH2) cell responses and allergic disease such as atopic eczema[4]. In addition, nerve fibres in the skin produce neuropeptides, which can activate immune cells and induce inflammation. The TH2 cytokines IL-4, IL-13 and IL-31 generated by immune cells can activate nerve endings and increase itching, resulting in a vicious itch-scratch cycle that deteriorates skin integrity[5] **(Figure 1)**. More recently, the OX40–OX40 ligand (OX40L) axis has been identified as a costimulatory pathway that promotes immune responses resulting in persistent skin inflammation in AD. Under inflammatory conditions, OX40L is upregulated on antigen-presenting cells (APCs) following antigen presentation, contributing to the activation of antigen-specific TH2 and TH1/TH17/TH22 cells and secretion of proinflammatory cytokines[6]. A recent multi-ancestry genome-wide association meta-analysis of 56,146 AD cases and 602,280 controls, found 101 genome-wide significant loci associated with AD, with 15 loci that have not been previously reported. Using a cell-type enrichment analysis, T cells were identified as the top enriched cell type in AD[7]. Taken together, T-cell-mediated processes are the main drivers of pathogenic hyperinflammation in AD and, at the same time, the main targets of current AD therapy.

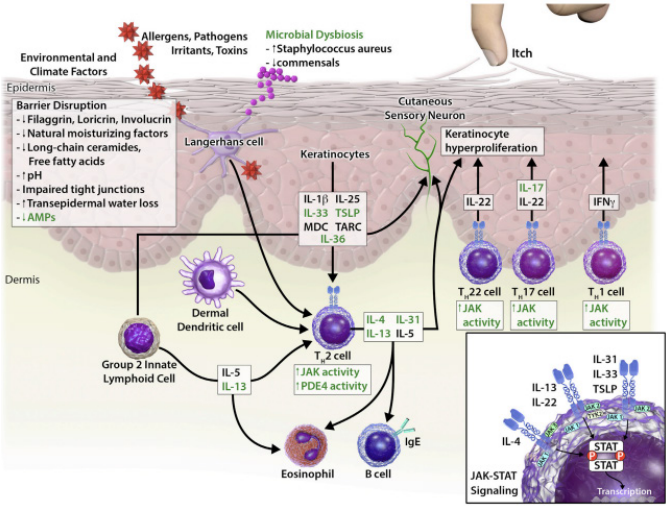


Figure 1: Pathogenesis of atopic dermatitis[5].

AMP = adenosine monophosphate, IFN = interferon, IL = interleukin, JAK = Janus kinase, MDC = macrophage-derived chemokine, STAT = signal transducer and activator of transcription proteins, TARC = thymus and activation-regulated chemokine, TSLP = thymic stromal lymphopoietin (also known as chemokine CCL17)[5].

2. Management of Atopic Dermatitis

Management of AD is individual and should be tailored to the respective patient. Joint decision-making between doctor and patient is important. Treatment of AD consists of a basic therapy (emollients to support the skin barrier); topical therapy (glucocorticoids, calcineurin inhibitors) and in more severe cases systemic therapy (glucocorticoids, biologics, Janus kinase inhibitors). Compliance to proactive therapy (long-term use of topical anti-inflammatory agents on affected skin areas, combined with emollients to prevent recurrence) and in general a healthy lifestyle is crucial to reduce frequency of flares. Atopic dermatitis may regress in adulthood, but many patients experience persistent or recurrent symptoms and AD may worsening due to stress, climatic factors and infections, often associated with other atopic diseases such as asthma, allergic rhinitis, food allergies; increased risk of mental disorders and sleep disorders.

Regular clinical assessments should include a periodical monitoring of the skin through physical examination to assess the severity and progress of the eczema. The use of objective scores is recommended to evaluate lesion extent, severity and quality of life impact. Objective severity scores, such as the eczema area and severity index (EASI), SCORing atopic dermatitis (SCORAD), investigator's global assessment (IGA) and patient-oriented eczema measure (POEM), enable personalized treatment plans and enhance research comparability. The EASI score integrates body surface area and skin lesion intensity into a single composite score. The EASI assesses only active acute or chronic AD lesions, while the SCORAD also assesses dry skin, pruritus and insomnia[8] **(Table 1)**. In addition, the Peak Pruritus Numerical Rating Scale (PPNRS) can help to quantify and track itch relief and is frequently used as a patient-reported outcome in clinical trials. The PPNRS is a well-defined, reliable, fit for

purpose measure to evaluate patient-reported intensity of worst itch in the previous 24 h for adults with moderate-to-severe atopic dermatitis. Clinical response is indicated by a ≥ 2–4-point change from baseline in the PP-NRS score[9].

Table 1: Commonly used severity scores for atopic dermatitis[8].

Score	Assessment criteria	No eczema	Slightly detectable eczema	Mild	Moderate	Severe	Very Severe
EASI	Extent (0–100%), Severity of lesions (0–12)	-	-	0-7	8-21	22-48	49-72
SCORAD	Extent (0–100%), Intensity (0–3), Subjective symptoms (0–4)	-	-	0-24	25-49	50-74	75-103
IGA	Overall severity	0: Clear	1: Almost clear	2: light pink, slightly raised	3: pink, moderately raised	4: deep pink, greatly raised	5: fiery red, greatly raised
POEM	Patientreported symptoms (7 items, 0–4), Impact (7 items, 0–4)	0–2: Clear or almost clear		3-7	8-12	13-18	19-28

EASI = eczema area and severity index, SCORAD = SCORing atopic dermatitis, IGA = investigator's global assessment, POEM = patientoriented eczema measure

3. Treatment of Adults with AD

Basic measures include the regular use of moisturisers to strengthen the skin barrier, appropriate skin cleansing (e.g., short baths) and avoidance of triggers. The recent updates of the European and US-American guidelines on the management of AD adhere to a stepwise treatment approach, starting with topical therapies and extending to systemic therapies in moderate to severe cases[10,11] **(Figure 2)**. Acute flare-ups are treated with topical corticosteroids, supplemented with non-steroidal creams containing calcineurin inhibitors such as tacrolimus or pimecrolimus if necessary. Antimicrobial therapy can be necessary, especially for infections with Staphylococcus aureus. Frequent local antimicrobial therapy should be avoided to prevent antimicrobial resistances; systemic antibiotics are used only for large-area infections. Systemic therapy is required if the symptoms cannot be controlled sufficiently with topical treatments and UV-B small band light therapy. However, phototherapy must not be used in patients with a history of skin cancer or with an increased risk of skin cancer (including photodamaged skin and those on systemic immunosuppressants). Topical steroids must be used with care to avoid skin thinning. Topical antibiotic, antiviral or antifungal treatments should be administered only for the treatment of superinfections of the skin, not for the treatment of atopic dermatitis itself. In severe cases, systemic medications such as conventional systemic immunosuppressants (CSI), monoclonal antibodies targeting inflammatory cytokines (biologics) or JAK inhibitors (JAKi) may be considered. The JAK inhibitors baricitinib, abrocitinib and upadacitinib are fast-acting, whereas the TH2-responses blocking antibodies dupilumab (targeting IL-4 receptor-alpha subunit, IL-4Rα), tralokinumab and lebrikizumab (both targeting IL-13), as well as the recently approved nemolizumab (targeting IL-31 receptor-alpha subunit, IL-31Rα) need some weeks to reach full efficacy. CSI such as cyclosporine and systemic corticosteroids have a rapid onset of action and can be used to treat flares or to bridge the time until onset of action of slower acting systemic immunosuppressants such as methotrexate (MTX) and azathioprine (AZT), both of them can be used off-label in the clinics. MTX must not be used during pregnancy in contrast to AZT. Oral corticosteroids should only be used as rescue medication for a short period of time to avoid side effects.

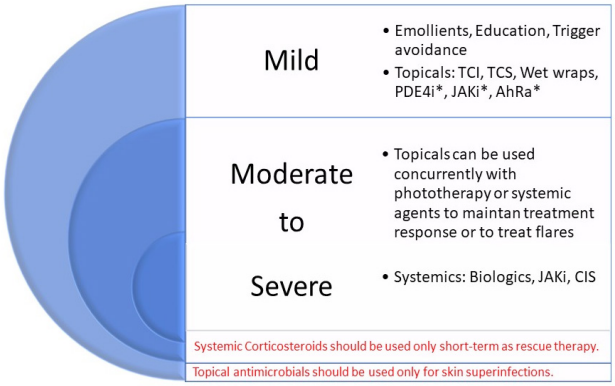


Figure 2: Stepped-care plan for adults, children and adolescents with atopic dermatitis[10-12].

*Crisaborole ointment, roflumilast cream, ruxolitinib cream, difamilast ointment, ruxolitinib cream and tapinarof cream with marketing authorisation for atopic dermatitis in the USA but not in Europe.

Abbreviations: AhRa = aryl hydrocarbon receptor agonist, CIS = conventional immunosuppressants, JAKi = JAK inhibitors, PDE4i = PDE4 inhibitors, TCI = topical calcineurin inhibitors, TCS = topical corticosteroids[10-12].

4. Treatment of Children and Adolescents with AD

About 80% of AD patients are identified in the early childhood and the comorbidity with asthma is a common allergic condition. A significant proportion of children shows symptoms before 12 months of age (approximately 60 %) and close to 80% before the age of 6[1]. While it often improves or goes away as children get older, it can persist into adulthood or, less commonly, have its first onset in adult life. Thinking about 50 years ago parents treated their children with fatty and oily zinc ointments, oak bark pouches to achieve itch relief or 'Cramer bandages' to protect the child's body against scratching. Nowadays, more solutions for everyday use are available such as soft cotton gloves protecting from scratching and several basic care products (gentle, moisturizing products) to be used after washing immediately after getting up and again in the evening before going to bed.

Nowadays, treatment options for children with moderate to severe AD have expanded enormously: the anti-IL-4Rα antibody dupilumab is available for children older than 6 months, the two IL-13 antibodies tralokinumab and lebrikizumab and the IL-31Rα antibody nemolizumab are available from the age of 12 years. From the group of JAK inhibitors, baricitinib is approved

(in Europe and more than 30 countries worldwide except the USA) from the age of 2 and upadacitinib and abrocitinib from the age of 12 for the treatment of children with moderate to severe AD. The approval of these systemic therapies represents a major change in the lives of severely affected children, which has a significant impact on their social participation and educational success. Overall, the side effect profile of systemic drugs in children is generally better than in adults, with specific challenges being the planning of live vaccinations and the administration of injections. The European Guideline on Atopic Eczema also recommends a stepwise treatment approach for paediatric AD patients, starting with topical therapies in mild AD and extending to systemic therapies for moderate to severe AD, similar to the recommendations for adults, except that systemic corticosteroids and PUVA-phototherapy should be avoided[10]. Similarly, the American Academy of Dermatology has recently issued the first-ever paediatric AD guidelines, highlighting prevention strategies and a stepwise approach of effective treatments including recently FDA approved topical therapies such as roflumilast, ruxolitinib and tapinarof creams[12] **(Figure 2)**.

5. Modulation of Skin Microbiome

Imbalances in the skin microbiome are often observed in AD. Unhealthy dietary patterns, such as those high in processed foods or low in essential nutrients (e.g., folate, vitamin D) may lead to systemic inflammation, gut dysbiosis and innate immune dysregulation, both resulting in a reduced production of essential antimicrobial peptides (AMPs) by keratinocytes, skin dysbiosis and susceptibility to skin infections. In particular, colonization with the common bacteria Staphylococcus aureus (S. aureus) is more frequent in severe AD. Approximately 30-60 % of AD patients have alpha toxins produced by S. aureus and its various strains that trigger immune system responses causing inflammation, itch and sometimes infection[13]. Unfortunately, there is an increased prevalence of AD skin infections caused by methicillin-resistant *S. aureus (MRSA)*, which is difficult to eliminate and can become life-threatening[14]. Restoring the skin microbiome can be achieved by topical and systemic treatments for AD as well as through dietary products such as probiotics, modulation of skin-pH and microbiome-based treatments, all of them are considered a promising approach for personalized treatment[15] **(Figure 3)**. Supplementation with vitamin D and vitamin E has also been shown to help reduce AD symptoms[16,17]. However, a systemic review on dietary supplements including fish oil, vitamin D or vitamin E found no convincing evidence of the benefit of dietary supplements in AD[18].

6. Approved Systemic Therapies

An overview of systemic therapies already approved or established in the management of patients with moderate-to severe AD in Europe and in the USA is given in **(Table 2)**.

Table 2: Systemic therapies for adults, children and adolescents with moderate-to-severe atopic dermatitis.

Product Class/Product	Approval Year EMA/FDA	Standard Dosing Regimen	Intensified Dose Regimen
Conventional Systemic Immunosuppressants (Generics)			
Cyclosporine	2013 (EMA) Off-label (FDA)	2.5-5 mg/kg per day in two single oral doses for 2-8 weeks	5 mg/kg per day in two single oral doses for up to 1 year
Methotrexate*	Off-label	5-15 mg/ week PO or SC	Up to 25 mg/ week PO or SC
Azathioprine	Off-label	0.5-3 mg/kg per day based on TPMT genotype for a period of 3 months Note: Patients with allele variants TPMT*2, *3A, *3B and *3C have low TMPT activity are at higher risk for toxic side effects [117]Brockmöller & Tzvetkov, 2008]. The dose must be adjusted to TPMT activity. Patients with no TPMT activity must not receive azathioprine.	
Corticosteroids	Unspecific license	Due to their side effects oral steroids should only be used up to 1 mg/kg per day for short periods of time (only rescue therapy)	
Biologics			
Dupilumab (Dupixent®)	2017 (EMA) 2017 (USA)	Adults: 600 mg SC on day 1 followed by 300 mg SC Q2W. Remission is expected after 4-6 weeks. Children > 6 months and adolescents: Weight based dosing regimens. Discontinuation in case no remission is achieved after 16 weeks.	In case of partial response after 16 weeks, continuation with 300 mg SC Q2W can be considered.
Tralokinumab (Adtralza®)	2021 (EMA) 2021 (FDA)	Adults and adolescents > 12 years: 600 mg SC on day 1 followed by 300 mg SC Q2W. Remission is expected after 4-8 weeks. Discontinuation in case no remission is achieved after 16 weeks.	In case of partial response after 16 weeks, continuation with 300 mg SC Q2W can be considered.
Lebrikizumab (Ebglyss®)	2023 (EMA) 2024 (FDA)	Adults and adolescents > 12 years and ≥40 kg body weight: 500 mg SC on day 1 and day 15 followed by 250 mg SC Q2W. Remission expected after 4-6 weeks, then maintenance dose of 250 mg SC Q4W. Discontinuation in case no remission is achieved after 16 weeks.	In case of partial response after 16 weeks, continuation with 250 mg SC Q2W up to week 24 can be considered.
Nemolizumab (Nemluvio®)	2024 (FDA) 2025 (EMA)	Adults and adolescents > 12 years and ≥ 30 kg body weight: 60 mg SC on day 1 followed by 30 mg SC Q4W for 16 weeks. Discontinuation in case no remission is achieved after 16 weeks.	In case of (partial) remission after 16 weeks continuation with 30 mg SC Q8W can be considered.
JAK-Inhibitors			
Baricitinib* (Olumiant®)	2020 (EMA) Off-label (FDA)	Adults, adolescents and children > 2 years and ≥ 30 kg body weight: 4 mg QD PO (2 mg QD PO for children <30 kg body weight and for patients with higher risk for VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections). Remission expected after 1-2 weeks, then maintenance dose of 2 mg QD PO.	If disease control is not maintained after dose reduction, re-treatment with 4 mg QD PO can be considered. Discontinuation in case no remission is achieved after 8 weeks of treatment.

Product Class/Product	Approval Year EMA/FDA	Standard Dosing Regimen	Intensified Dose Regimen
Abrocitinib* (Cibinqo®)	2021 (EMA) 2022 (FDA)	Adults and adolescents > 12 years: 100 mg or 200 mg QD PO (based on individual patient risk for VTE, MACE and malignancy). Remission expected after 1-2 weeks, then maintenance dose of 100 mg QD PO. Discontinuation in case no remission is achieved after 24 weeks of treatment.	If disease control is not maintained after dose reduction, re-treatment with 200 mg QD PO can be considered.
Upadacitinib* (Rinvoq®)	2021 (EMA) 2022 (FDA)	Adults and adolescents > 12 years: 30 mg QD PO (15 mg QD PO for patients with body weight < 30 kg or higher risk for VTE, MACE and malignancy, for patients aged ≥ 65 years). Remission expected after 1-2 weeks. The lowest effective maintenance dose should be used to maintain disease control. Discontinuation in case no remission is achieved after 3 months of treatment.	

* Contraindicated in pregnancy and lactation. Abbreviations: BID = twice daily, IV = intravenous, JAK = Janus kinase, MACE = major cardiovascular events, PO = per os, QD = once daily, Q2W = every 2 weeks, Q4W = every 4 weeks, Q8W = every 8 weeks, SC =subcutaneous, TMPT = Thiopurin-S-Methyltransferase, VTE = Venous thromboembolism

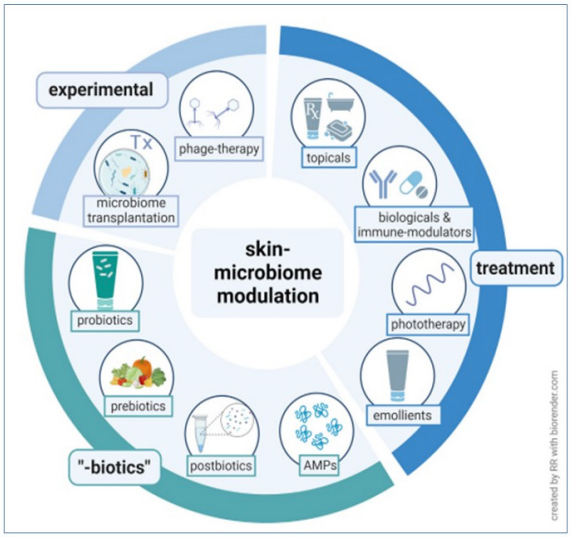


Figure 3: Modulation of skin microbiome by different therapeutic approache[15].

6.1. Monoclonal antibodies

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling. The TH2 cytokines IL-4 and IL-13 interact with heterodimeric IL-4 receptor (IL-4R) complexes triggering transphosphorylation and transactivation of the JAK/STAT signalling pathway, which is a key driver of acute and chronic inflammatory processes in AD. Dupilumab can inhibit IL-4 signalling via the Type I IL-4R (IL-4Rα/γc) and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα1) depending on the abundance of the IL-4Rα and IL-13Rα1 subunits in the target cells[19]. Dupilumab was approved by EMA (2017) as Dupixent® for adults with moderate-to-severe AD to be administered 300 mg every 2 weeks based on the SOLO clinical trial program[20,21]. In the SOLO-CONTINUE trial, high-responding patients treated with dupilumab in SOLO were rerandomized 2:1:1:1 to continue their original regimen of dupilumab, 300 mg, weekly or every 2 weeks or to receive dupilumab, 300 mg, every 4 or 8 weeks or placebo for 36 weeks. However, longer dosage intervals and placebo resulted in a diminution of response for all end points. Hence, the approved regimen of 300 mg of dupilumab every 2 weeks is recommended also for long-term treatment[22]. Conjunctivitis is a common side effect of dupilumab, with incidence rates ranging from 7.9% to 19.4%in adults and from 4.8 to 14.8% in paediatric populations[23]. Therefore, patients receiving dupilumab should be monitored for ocular symptoms and appropriate management should be provided.

Stapokibart (CM310) is a humanized monoclonal antibody which similar to dupilumab is targeting the IL-4 receptor-α subunit (IL-4Rα), a shared receptor for IL-4 and IL-13 which are key pathogenic drivers of AD. In the phase 3 induction trial (NCT05265923), significant higher proportions of adult AD patients receiving stapokibart (300 mg every 2 weeks) achieved ≥75% improvement over placebo from baseline in EASI-75 (66.9% vs. 25.8%) and IGA score of 0/1 with ≥2-point reduction (44.2% vs. 16.1%) at Week 16. In addition, continued stapokibart treatment induced sustained improvements in AD signs and symptoms without new safety signals during the maintenance treatment period over 52 weeks in adults with moderate-to-severe AD[24]. Based on these positive data of the pivotal trials, the National Medicinal Products Administration (NMPA) of China has approved stapokibart (trade name: Kangyueda) for the treatment of adults with moderate to severe AD.

Rademikibart (previously CBP-201) is a fully human monoclonal IgG4kappa (IgG4κ) antibody blocking IL-4 receptor alpha (IL-4Rα) able to engage fully with IL-4 and IL-13 interaction domains, including domain 1, domain 2 and a small hinge region. It is a second-generation IL-4Rα inhibitor that exhibits twice the binding affinity to IL-4Rα compared to dupilumab, due to its optimized epitope design[25]. In the pivotal trial (NCT05017480, SEASIDE CHINA), a significant percentage of patients with moderate-to-severe AD who were treated with rademikibart 300 mg every 2 weeks reached all primary and secondary endpoints (e.g., vIGA 0/1, EASI, PP-NRS) at week 16[26]. Most patients with response at Week 16 maintained them through Week 52[27,28]. Based on these positive results, the Chinese National Medical Products Administration (NMPA) approved rademikibart for the treatment of adults with moderate to severe AD in July 2025.

Tralokinumab is a fully human IgG4 monoclonal antibody that binds to IL-13 with exceptionally high affinity, which prevents the interaction of IL-13 with the IL-13Rα1 and with the heterodimer IL-13 Rα1/IL-4Rα but not with the IL-13Rα2. Thus, any IL-13 that is not bound by tralokinumab (i.e., free IL-13) can be bound by IL-13Rα2 and subsequently internalized, regardless of the presence of tralokinumab[29]. Tralokinumab was approved by EMA (2021) as Adtralza® for the treatment of moderate-to-severe AD in adults based on the data of the phase 3 program (ECZTRA 1, ECZTRA 2 and ECZTRA 3 trials). In the two identical ECZTRA 1&2 trials, tralokinumab 300 mg Q2W was significantly superior to placebo with respect to improvements in primary endpoints IGA 0/1 and EASI-75 after 16 weeks and secondary endpoints in the 16-week analysis (including pruritus scores, DLQI, SCORAD, EASI-50 and EASI-90 and eczema-related sleep interference)[30]. The ECZTRA 3 trial was designed

based on real-world experience as it introduced systemic therapy with tralokinumab 300 mg every two weeks in combination with mometasone furoate 0.1 % cream (once daily to active lesions as needed) in moderate to severe AD patients who were inadequately controlled by topical therapy and systemic corticosteroids. This combination of tralokinumab and topical mometasone furoate improved EASI-75 and IGA 0/1 at week 16 significantly compared with placebo: 56.0 versus 35.7 % ($P < 0.001$) and 38.9 versus 26.2 % ($P = 0.015$), respectively. Clinical benefits were also reported for secondary endpoints at week 16 such as EASI-90 (32.9 versus 21.4 %; $P = 0.022$) and EASI-50 (79.4 versus 57.9 %; $P < 0.001$)[31].

Lebrikizumab is an IgG4 monoclonal antibody that binds with high affinity to interleukin IL-13 and selectively inhibits IL-13 signalling through the IL-4 receptor alpha (IL-4Rα)/ IL-13 receptor alpha 1 (IL-13Rα1) heterodimer, thereby inhibiting the downstream effects of IL-13. Lebrikizumab does not prevent the binding of IL-13 to the IL-13Rα2 (decoy receptor), which allows the internalisation of IL-13 into the cell. In 2023, the EMA approved lebrikizumab (EbGLYSS®) for the treatment of moderate-to-severe AD in adults and adolescents aged 12 and older, weighing at least 40 kg, who are candidates for systemic therapy[32]. The market authorisation was given due to the results of the ADVOCATE program including three phase 3 trials. In the first study, involving 424 patients with AD, 43% of patients who received lebrikizumab achieved an IGA score of 0 or 1 compared with 13% of patients who received placebo. In addition, 59% of patients achieved EASI-75 with lebrikizumab compared with 16% of patients on placebo. In the second study, involving 445 patients with AD, 33% of patients had an IGA score of 0 or 1 with lebrikizumab compared with 11% of patients on placebo. In addition, 52% of patients receiving lebrikizumab achieved EASI-75 compared with 18% of patients receiving placebo. In the third study, involving 228 AD patients who were also given topical corticosteroids, 41% of patients given lebrikizumab and corticosteroids had an IGA score of 0 or 1 and 70% achieved EASI-75. The results for patients given placebo and corticosteroids were 22% and 42% respectively. In terms of long-term treatment, the beneficial effect of lebrikizumab was maintained up to 52 weeks in patients who achieved IGA 0 or 1 and EASI-75 at week 16. The most common side effects with lebrikizumab (which may affect up to 1 in 10 people) include injection site reactions, dry eye and conjunctivitis including allergic conjunctivitis[33]. Long-term studies of up to 3 years report sustained efficacy and a consistent safety profile and tolerability over time[34].

Nemolizumab is a humanised IgG2 monoclonal antibody that inhibits interleukin-31 (IL-31) signalling by binding selectively to IL-31 receptor alpha (IL-31Rα). IL-31 is belonging to the IL-6 cytokine family and is deriving from TH2 cell responses. The IL-31 receptor is a heterodimer, consisting of the IL-31Rα chain and oncostatin M receptor β-chain (OSMR-β). IL-31 induces a signal transduction pathway through the JAK/STAT, phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways[35]. It is involved in the underlying mechanisms of AD and specifically associated with pruritus, inflammation, epidermal dysregulation and fibrosis[36-38]. In AD clinical trials, nemolizumab was found to modulate gene expression related to the pathophysiology of AD by decreasing the inflammatory and proliferative profile of T-cells and monocytes/ macrophages without leading to immunosuppression. In February 2025, the European Commission approved nemolizumab as Nemluvio® for moderate to severe AD in patients aged 12 years and older due to its effectiveness demonstrated in the phase 3 ARCADIA program with the advantage of once monthly dosing compared to twice monthly dosing required for dupilumab, lebrikizumab and tralokinumab[39]: ARCADIA 1 and ARCADIA 2 enrolled a total of 1728 subjects 12 years of age and older with moderate-to-severe atopic dermatitis not adequately controlled by topical treatments. Disease severity was defined by an IGA score of 3 (moderate) and 4 (severe), an EASI score of at least 16, a minimum BSA involvement of 10% and a PPNRS score of at least 4. Subjects in the studies received initial subcutaneous (SC) injections of either nemolizumab 60 mg, followed by 30 mg injections every 4 weeks or matching placebo. Nemolizumab was statistically significant superior to placebo with respect to skin-related co-primary endpoints IGA success (score of 0 or 1 with ≥2-point improvement) and EASI-75 over 16 weeks. Results for both co-primary endpoints were consistent in the severe pruritus population (baseline PPNRS ≥ 7) **(Figure 4)**. The most common side effects with nemolizumab included hypersensitivity reactions and injection site reactions. Formation of anti-drug-antibodies was frequently observed, but without affecting its pharmacokinetics, safety or efficacy. In the ARCADIA long-term extension trial (NCT03989206), treatment with 30 mg nemolizumab every 4 weeks maintained significant and progressive improvements in disease activity, itch, sleep and quality of life for up to 104 weeks. The safety profile of nemolizumab remained stable, with no new safety signals observed[40].

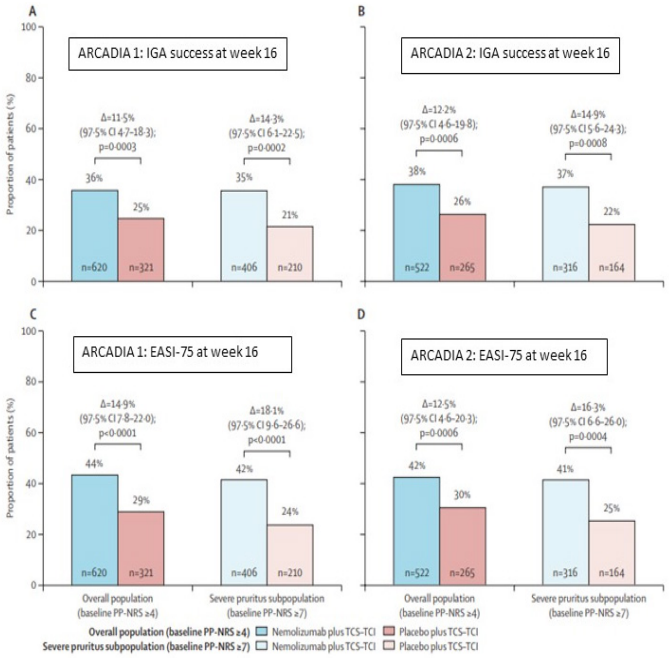


Figure 4: Coprimary endpoints in ARCADIA 1 and ARCADIA 2[39].

Non-responder imputation analysis was used. Adjusted effect sizes (percentage difference with 97·5% CIs) and p values versus the placebo group are from a Cochran– Mantel–Haenszel test adjusting for the randomisation stratification variables. EASI=Eczema Area and Severity Index. IGA=Investigator's Global Assessment. n=number of participants with data after imputation. PP-NRS=Peak Pruritus Numerical Rating Scale. TCI=topical calcineurin inhibitors. TCS=topical corticosteroids[39].

7. JAK Inhibitors

The Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway play a crucial role in cytokine signalling and regulates the functions of TH1, TH2, TH17 and TH22 cells, which are involved in the inflammatory pathogenesis of AD. The JAK family of enzymes consists of four members, JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) which work in pairs to phosphorylate and activate one or more of the seven transcription factors of the STAT family (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6) which modulate gene expression and cellular functions. The TH2 cytokines IL-4, IL-13 and IL-31 are signalling via transmembrane receptors coupled to the JAK/STAT pathway and are also driving itch, the main symptom of AD. TYK2 acts as an intracellular signalling enzyme and is crucial for signalling pathways of IL-12/Th1/, IL-23/Th17, as well as type I IFN cell responses and may provide new alternatives for AD treatment[5]. Since JAK inhibitors are small molecules that can be taken orally, they work faster to relieve symptoms, especially itching, compared to some other treatments. Unlike monoclonal antibodies that target only one or two specific cytokines, JAK-inhibitors block multiple signalling pathways at once, making them highly effective against a wide range of inflammatory signals in AD. By achieving a broad, intermittent inhibition of the activity of multiple cytokines, JAK inhibitors help to modulate TH2 cell-mediated inflammation, epidermal barrier dysfunction and itch signalling. This comprehensive blockade, however, can affect essential immune functions, which may lead to an increased risk of severe infections. In addition, FDA still requires warnings about an increased risk of serious heart-related events, cancer, blood clots and death for JAK inhibitors in the treatment of inflammatory conditions including AD[41]. The warning was prompted primarily from tofacitinib studies in rheumatoid arthritis, an assumed class effect and the absence of long-term safety data for recently approved oral JAK-inhibitors. At present, three systemic oral JAK-inhibitors including baricitinib, abrocitinib and upadacitinib have received approval for systemic use in moderate to severe AD whereas ruxolitinib and delgocitinib have been recently approved for topical AD treatment[42] **(Figure 5)**.

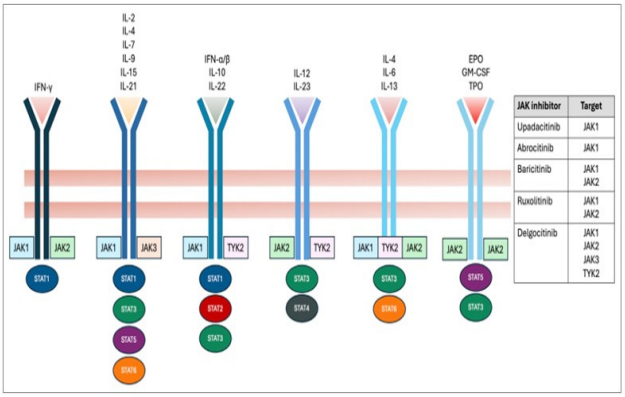


Figure 5: Mechanism of action of approved JAK inhibitors[42].

JAK inhibitors inhibit different combinations of JAK intracellular proteins. Upon binding of a cytokine to its receptor, intracellular JAK proteins mediate recruitment and tyrosine phosphorylation of STAT proteins. Phosphorylated STAT proteins dimerize and translocate to the nucleus, where they regulate different genes.

Abbreviations: IFNg = interferon gamma, IL = interleukin, JAK = Janus kinase, STAT = signal transducer and activator of transcription, TYK2 = tyrosine kinase 2[42].

Baricitinib (Olumiant®) is a selective and reversible inhibitor of JAK1 and JAK2 thereby reducing the phosphorylation and activation of STATs. In the pivotal phase 3 study (BREEZE-AD7), baricitinib in combination with topical corticosteroids showed significant effects compared to placebo for the primary endpoints at week 16: a vIGA for AD score of 0 (clear) or 1 (almost clear) was achieved by 31% of patients receiving 4 mg of baricitinib, 24% receiving 2 mg of baricitinib compared with 15% receiving placebo, all three groups received also topical corticosteroid therapy[43]. Baricitinib was the first systemic JAK1/JAK2 inhibitor approved by EMA in 2020 for the treatment of mild-to-moderate AD. Except the USA, it has been approved for treating moderate to severe AD in adult patients in more than 70 countries and in over 30 countries for adolescents and children from age 2 years with moderate to severe AD, who are candidates for systemic therapy[44]. In 2024, a final integrated safety analysis of baricitinib therapy in moderate-to-severe AD was published, including data from eight trials from the BREEZE program with a duration of up to 200 weeks, resulting in a maximum exposure of 4.6 years of therapy. Rates of major adverse cardiovascular events, deep vein thrombosis/pulmonary embolism, malignancies and serious infections were within ranges of background rates in patients with AD. These outcomes continue to demonstrate a consistent and well established safety profile for baricitinib, with no new safety signals[45].

Abrocitinib (Cibinqo®) is a selective JAK1 inhibitor preventing the phosphorylation and activation of STATs. Abrocitinib showed significant efficacy compared to placebo in the JADE (JAK1 Atopic Dermatitis Efficacy and Safety) clinical phase 3 program, which consisted out of the JADE MONO-1 (NCT03349060) and the JADE MONO-2 (NCT03575871) trials in subjects aged 12 years and older with moderate to severe AD[46,47]. In addition, in the active comparator trial JADE COMPARE (NCT03720470) abrocitinib was tested against placebo or dupilumab in adult subjects with moderate to severe AD on background topical therapy[48]: The two primary endpoints at Week 12 were met: (i) proportion of patients achieving an IGA score of 0 (clear) or 1 (almost clear), with an improvement from baseline (IGA 0/1) and (ii) the proportion of patients achieving improvement in the EASI-75 score. The key secondary endpoint was the proportion of patients achieving point improvement on the Peak Pruritus Numerical Rating Scale (PP-NRS) at Week 2 and Week 12, demonstrating a rapid and substantial reduction in itch compared to placebo. Treatment with abrocitinib at a dose of either 200 mg or 100 mg once daily resulted in significantly greater reductions in signs and symptoms of moderate-to-severe AD than placebo at weeks 12 and 16. The 200-mg dose, but not the 100-mg dose, of abrocitinib was superior to dupilumab with respect to itch response at week 2. Neither abrocitinib dose differed significantly from dupilumab with respect to most other key secondary end-point comparisons at week 16.

Upadacitinib (Rinvoq®) is a selective and reversible JAK1 inhibitor. In human cellular assays, upadacitinib selectively inhibits signalling by JAK1 and JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibiting JAK1 with upadacitinib reduces the signalling of many mediators which drive the signs and symptoms of AD such as eczematous skin lesions and pruritus. The efficacy and safety of upadacitinib 15 mg and 30 mg once daily has been demonstrated in three phase 3 studies (MEASURE UP 1, MEASURE UP 2 and AD UP) in adult and adolescent patients

with moderate to severe AD not adequately controlled by topical medications. A significantly greater proportion of patients treated with upadacitinib 15 mg or 30 mg achieved vIGA-AD 0 (clean) or 1 (almost clean), EASI 75 or a ≥ 4-point improvement on the Worst Pruritus NRS compared to placebo at week 16. Rapid improvements in skin clearance and itch were also achieved[49].

8. Approved Topical Therapies

Most topical treatments for AD are generic products such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI). TCS are used for short-term treatment of inflammatory flare-ups, while TCI are an alternative, especially for sensitive skin areas. New developments include topical JAK inhibitors and phosphodiesterase 4 (PDE4) inhibitors, which have demonstrated significant results in both adult and paediatric patients whilst possessing a favourable safety profile. The JAK inhibitors ruxolitinib and delgocitinib and the PDE4 inhibitors crisaborole, roflumilast and difamilast have already received approval as topical AD treatments by the US-FDA and/or the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) but not by the EMA. The American Academy of Dermatologists strongly recommends topical treatment of inflamed areas with ruxolitinib cream for children older than 12 years with mild-to-severe AD as it effectively decreases the severity of the dry and itchy skin. An overview of topical therapies which have been already approved or established in the management of patients with atopic dermatitis is given in **(Table 3)**.

Table 3: Approved topical treatments for adults, children and adolescents with AD.

Topical Product	Approvals EMA/FDA/PMDA	Dosing Recommendations
Corticosteroids		
Topical Corticosteroids with different therapeutic index	More than 30 generic products for skin diseases including AD	In general, TCS only for treatment of acute flares for a short period of time: Potent to very potent TCS for adolescents and adults and children up to 2 years under specialist supervision Low to moderate potency TCS can routinely be used for patients ≥ 2 years. For children < 2 years, any TCS treatment should be under specialist supervision.
Calcineurin Inhibitors		
Tacrolimus	Several generic products for moderate to severe AD when TCS treatment is not sufficient or not possible	Tacrolimus 0.03% ointment for adults and children ≥ 2 years Tacrolimus 0.1% ointment for patients ≥16 years
Pimecrolimus	Several generic products for mild to moderate AD when TCS treatment is not sufficient or not possible	Pimecrolimus 1% cream for patients aged 3 months and older
JAK-Inhibitors		
Ruxolitinib	FDA (2020): OPZELURA® approved for mild to moderate AD in adults FDA (Sep 2025): OPZELURA® approved for AD in children	1.5% cream for adults and adolescents (≥12 years) to be applied twice daily -up to 20 % BSA (not more than 60 gram per week) 1.5% cream for children 2-11 years to be applied twice daily (not more than 60 gram per 2 weeks)
Delgocitinib	PMDA (2020): CORECTIM® for adult and paediatric AD EMA (2024): ANZUPGO® for moderate to severe hand eczema	0.5 % ointment for adults twice daily (not exceeding 5 g at a time) 0.25% ointment for children to be applied twice daily (not exceeding 5 g at a time) 2% cream for adults with hand eczema twice daily on affected skin of hands and wrists up to 12 weeks
PDE4 Inhibitors		
Crisaborole	FDA (2016): EUCRISA™ for adults, adolescents and children ≥ 2 years with ≤ 40% affected body surface area (BSA) EMA (2020): STAQUIS® Not marketed in EU due to withdrawal of MA by EC on request of Pfizer in 2022	2% ointment to be used twice daily up to 12 weeks
Difamilast	PMDA (2021): MOIZERTO® for adult and paediatric AD FDA (February 2026): ADQUEY™ for mild to moderate AD	1% ointment for adults and children ≥ 2 years twice daily 1% ointment for adults and children ≥ 2 years twice daily
Roflumilast	FDA (2024): ZORYVE® for adult and paediatric AD	0.15% cream for patients aged 6 years and older to be applied once daily 0.05% cream for children aged 2-5 years to be applied once daily
Aryl hydrocarbon receptor agonist		
Tapinarof	FDA (2024): VTAMA™ for patients aged 2 years and older with AD	1% cream to be applied to affected areas once daily

Abbreviation: AhR = aryl hydrocarbon receptor, EC = European Commission, JAK = Janus Kinase, PDE4 = Phosphodiesterase 4, PMDA = Pharmaceuticals and Medical Devices Agency (Japan).

Source: Based on European and US American guidelines for the management of atopic dermatitis[10-12] and the SMPCs of ANZUPGO®[67], ZORYVE®[75], VTAMA™[79], OPZELURA®[122], EUCRISA™[123], ADQUEY™[124] and the drug information sheet of CORECTIM®[125].

8.1. Topical Corticosteroids (TCS)

TCS have been the cornerstone of AD treatment for 40 years. Hydrocortisone was the first agent to be used; since then, around 30 other corticosteroid preparations have been approved for AD treatment. TCS are considered a first line treatment to reduce inflammation, pruritus and relapses and act for AD flares after basic management with moisturizers[50,10]. Corticosteroids are lipophilic and therefore penetrate the skin well where they bind to the steroid receptor in the cytoplasm of keratinocytes and fibroblasts within the epidermis and dermis. The corticosteroid-receptor complex translocates to the nucleus where it binds to the glucocorticoid-response element (a specific sequence of DNA) thereby inducing anti-inflammatory and metabolic proteins - called transactivation. In addition, corticosteroid molecules can interact directly or indirectly with regulatory genes for inflammation thereby downregulating proinflammatory transcription factors - called transrepression. TCS induced genomic (transactivation and transrepression) processes as well as non-genomic processes (vasoconstrictive effects) result in strong anti-inflammatory, anti-proliferative (antimitotic) effects but may also downregulate immune responses and inhibit T lymphocyte functions[51] **(Figure 6)**.

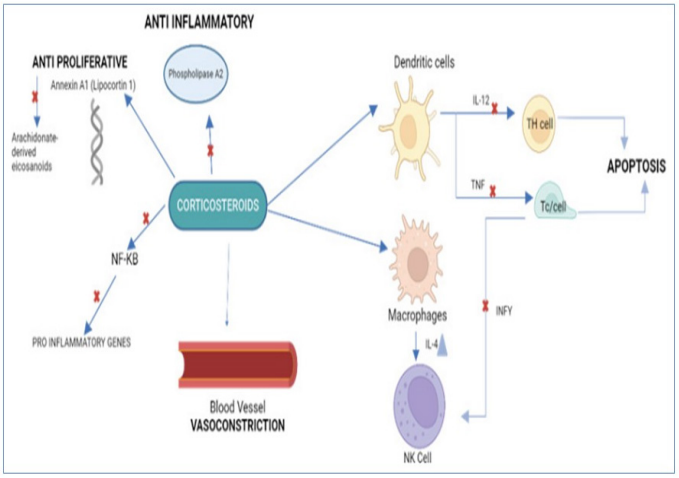


Figure 6: Genomic and non-genomic mechanisms of action of topical corticosteroids[51].

TCS were originally classified only by their potency based on the skin vasoconstriction assay, which measures skin blanching on topical application[52,53]. Most European countries are using the classification according to Niedner from mild (class I) to super-potent corticosteroids (class IV)[54] while the WHO classification allocates 7 groups starting from VII (weakest) to I (most potent)[55] which is used by US-American dermatologists. Today, TCS are classified by potency and the risk of side effects such as atrophy, striae, rosacea, teleangiectasias, purpura and other cutaneous and systemic reactions. A therapeutic index (TIX) has been introduced for TCS based on a concept of the benefit-risk ratio evaluation concerning both efficacy and safety[56]. The TIX is the ratio of desired versus adverse effects of the TCS. Since a TIX of 1–2 is defined as an equal relation of desired and adverse effects, a TIX of 2-3 indicates a TCS with improved benefit-risk ratio. For example, mometasone furoate, a class III corticosteroid with a TIX of 2 has stronger desired effects than adverse effects[57] **(Table 4)**.

Table 4: Classification of TCS based on therapeutic indices and their potential to induce skin atrophy.

TIX	Skin atrophy	Class	Glucocorticoid
1	1	I	Hydrocortisone
1.06	2	II	Triamcinolone acetonide
1.2	2	III	Betamethasone valerate
1.4	1	II	Hydrocortisone butyrate
1.5	2	IV	Clobetasol propionate
2	1	II	Prednicarbate
2	1	II	Methylprednisolone aceponate
2	1	III	Mometasone furoate

Class: I, weak; IV, very strong. TIX, therapeutic index: 1 ≤2 relation between desired and adverse effect is equal, 2-3 GC with improved benefit/risk ratio. Skin atrophy: 1, GC induces little skin atrophy; 2, GC induces much skin atrophy[57].

Low and medium potency TCS can be used for a longer duration with reduced atrophy risk compared to higher potency TCS. High and very high potency TCS should only be used to treat severe AD flares. The latest generation TCS with innovative vehicles such as nanocarrier show an improved pharmacokinetics and a better risk-benefit ratio and are therefore favoured over earlier generation TCS. Modern, double-esterified TCS (hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone butyrate, prednicarbate, methylprednisolone aceponate, mometasone furoate) have a pronounced anti-inflammatory effect but no strong antiproliferative properties with less potential for skin atrophy[57,58]. For the treatment of the face and neck, only weak to moderately potent corticosteroids should be used and for a few days only. TCS are usually applied in the ranges from twice weekly to once or twice daily for a two-week period.

9. Topical Calcineurin Inhibitors (TCI)

TCI such as tacrolimus and pimecrolimus have also immunosuppressive effects and inhibit T lymphocyte activation, but penetrate the skin less than corticosteroids. Therefore, they are the preferred treatment for sensitive skin areas such as face and neck. The anti-inflammatory effect of 0.1% tacrolimus ointment is comparable to that of a medium-strong TCS or 1% pimecrolimus cream[59].

9.1. Topical JAK Inhibitors (TJI)

TJI reduce signalling of key inflammatory cytokines such as IL-4, IL-13 and IL-31 involved in the pathogenesis of AD. Delgocitinib and ruxolitinib are effective in treating AD and significantly improved EASI, IGA, pruritus-NRS score in late phase clinical trials with adult AD patients. All topical JAK inhibitors show minimal risk of mild-to-moderate adverse effects.

Ruxolitinib (Opzelura®) is a topical JAK1/2-inhibitor that has shown similar or even higher efficacy in adults with mild-to-moderate AD compared to triamcinolone cream (group III TCS) and has been approved by the US-FDA for its use in the treatment of AD[60]. The 2023 AAD guidelines have given a strong recommendation for topical JAK inhibition with ruxolitinib 1.5% cream for mild to moderate AD in patients at least 12 years of age and up to 20% affected BSA without any topical drug interaction warning[50]. In 2024, the American Academy of Allergy, Asthma and Immunology (AAAAI) recommended topical ruxolitinib as effective for AD patients unresponsive to

conventional therapies or with contraindications to systemic immunosuppressants[61]. An updated systematic review and meta-analysis of five randomized clinical trials that enrolled patients predominantly with moderate-to-severe AD concluded that monotherapy with ruxolitinib cream does significantly improve moderate-to-severe AD, without a significant increase in adverse events across all age groups[62].

Delgocitinib (Anzupgo®) is a topical JAK1/2/3/TYK2 (pan)JAK-inhibitor which significantly improved pruritus and EASI in adult Japanese patients with moderate to severe AD[63]. Moreover, topical delgocitinib was observed to have a great efficacy in the treatment of AD in children in Japan[64]. In 2020, the Japanese PMDA approved delgocitinib for adult and paediatric AD patients as 0.5% and 0.25% CORECTIM® ointment, respectively. In the European Union, delgocitinib has been approved as a 2% creme (Anzupgo®) for the treatment of moderate to severe chronic hand eczema in adults for whom topical corticosteroids are not sufficient or are not suitable. The approval was based on the positive safety and efficacy outcomes of three phase 3 trials: adults with moderate to severe chronic hand eczema received twice-daily 2% delgocitinib cream or cream vehicle for 16 weeks (DELTA 1&2) and up to 52 weeks in the open-label extension trial (DELTA 3). The primary endpoint was the Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE), defined as IGA-CHE score of 0 (clear) or 1 (almost clear, defined as only barely perceptible erythema), which was met at week 16 and week 52, respectively[65,66]. The safety and efficacy of Anzupgo® in children and adolescents under 18 years of age have not been established so far[67].

10. Topical PDE4 Inhibitors (TPI)

Several TPI have been already approved for treatment of adult and paediatric patients with mild to moderate AD by the US-FDA (crisaborole, roflumilast and difamilast) and by the Japanese PMDA (difamilast). None of these TPI has currently a marketing authorisation in the European Union. The inhibition of PDE4 increases intracellular cyclic adenosine monophosphate (cAMP) levels. Drugs that elevate intracellular cAMP levels suppress immune functions of T cells, monocytes, macrophages and neutrophils, by reducing the production of pro-inflammatory cytokines and by increasing the production of anti-inflammatory mediators[68] **(Figure 7)**.

Crisaborole is a medium potent, selective PDE4 inhibitor (especially of the PDE4A subtype). It is a low molecular weight boron compound with a non-steroidal structure. Due to its small size, the active ingredient can penetrate the upper layers of the skin. In 2016, crisaborole 2 % ointment has been approved as EUCRISA™ by the US-FDA for treatment of mild to moderate AD in patients 2 years of age and older. The approval of EUCRISA™ is based on two phase 3 trials in which adult and paediatric patients with mild to moderate AD received either crisaborole 2% ointment or vehicle twice daily for 28 days. In both trials, the primary efficacy endpoint [improvement of the Investigator's Static Global Assessment (ISGA) score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at day 29] was met. Moreover, crisaborole demonstrated a favourable safety profile and reduction in overall disease severity, pruritus and other signs of AD[69]. Crisaborole has been approved in the European Union in 2020 but is not commercialized in Europe since the European Commission has withdrawn its marketing authorisation in 2022 at the request of the marketing authorisation holder, Pfizer Europe MA EEIG, which notified the European Commission of its decision not to market the product in the EU for commercial reasons.

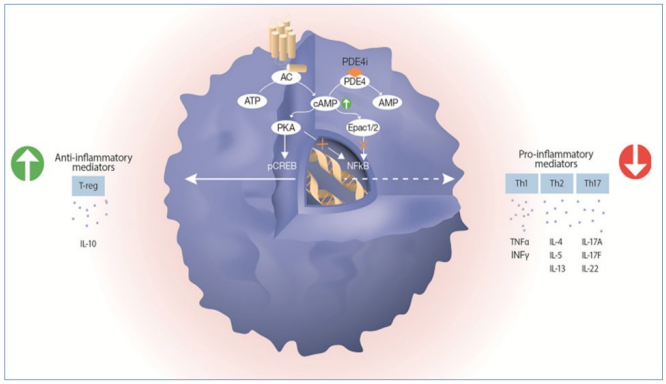


Figure 7: Immunomodulatory action of PDE4-inhibitors[68].

PDE4 inhibitors suppress inflammatory immune responses by elevating intracellular cAMP levels. Increased level of cAMP inhibits the production of pro-inflammatory cytokines through simultaneous inhibition of PKA-NFkB and Epac1/2-NFkB pathways; and promotes the production of anti-inflammatory mediators by activation of the PKA-CREB pathway. The intracellular level of cAMP is mainly controlled by the activity of adenylyl cyclase and PDE4. Abbreviations: adenylyl cyclase = AC, phosphodiesterase 4 = PDE4, protein kinase A = PKA, exchange protein 1/2 activated by cAMP = Epac1/2, phosphorylated cAMP-responsive element binding protein = pCREB, nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB), inhibitor of PDE4 = PDE4i[68].

Difamilast is a PDE4 inhibitor (especially of the PDE4B subtype) exerting mainly anti-inflammatory action by reducing inflammatory cytokines like TNFα and more effectively than other PDE4-inhibitors (CP-80633, cipamfylline and crisaborole)[70]. In the phase 3 program, 0.3% and 1% difamilast ointment twice daily has shown significant improvements compared to vehicle in the EASI and IGA scores in Japanese adult and paediatric AD patients at week 4[71,72] and up to 52-weeks[73]. In 2021, the Japanese PMDA approved 1% difamilast ointment as MOIZERTO® for the treatment of AD. In February 2026, the US-FDA has approved 1% difamilast ointment as ADQUEY™ for the treatment of mild-to -moderate AD in patients of 2 years of age and older.

Roflumilast is a highly potent PDE4-inhibitor without any particular selectivity for the various PDE4 isoforms (i.e., a pan-PDE4-inhibitor). In 2024, roflumilast received FDA approval as ZORYVE® 0.15% cream based on the results of two phase 3 vehicle-controlled studies (INTEGUMENT-1 and INTEGUMENT-2), which evaluated 1337 patients with mild to moderate AD ages 6 years and older. Patients applied ZORYVE cream 0.15% or vehicle once daily for 4 weeks. The primary endpoint (vIGA-AD at week 4) and the secondary endpoint (Peak Pruritus-NRS at week 4) were met. Roflumilast improved AD relative to vehicle cream, based on multiple efficacy end points, with favourable safety and tolerability[74]. In the following, a roflumilast 0.05 % cream has been approved for children in the age of 2-5 years based on the results of the phase 3 INTEGUMENT-PED trial, where the cream or vehicle was applied once daily for 4 weeks[75]. In March 2026, Arcutis announced new data from the INTEGUMENT-INFANT Phase 2 trial demonstrating that ZORYVE® cream 0.05% reduced signs and symptoms of AD in infants aged 3 months to less than 24 months with mild to moderate atopic dermatitis[76].

11. Topical Aryl Hydrocarbon Receptor Agonist

Tapinarof (3,5-Dihydroxy-4-isopropylstilben) is a fist-in-class, nonsteroidal small molecule agonist of the aryl hydrocarbon receptor (AhR), which has been originally isolated from metabolites of the bioluminescent bacterium Photorhabdus luminescens that lives symbiotic in the gut of insect-specific pathogenic nematodes. The anti-inflammatory and antibiotic properties of tapinarof confer a competitive advantage to organisms producing it over other bacteria and therefore prevent rapid insect putrefactio[77]. The AhR is a ligand-dependent transcription factor that plays a role in regulating cytokine and skin barrier protein expression as well as antioxidant activity[78] **(Figure 8)**. Tapinarof reduces TH2 and TH17 responses and modulates regulatory T cell (Treg) functions in inflammatory skin diseases like AD and psoriasis. Tapinarof restores the epidermal barrier through upregulation of protective proteins such as filaggrin, hornerin and involucrin and increases antioxidant responses via direct binding to nuclear transcription factor DNA recognition elements. In 2024, the US-FDA approved tapinarof 1% cream as VTAMA™ for patients aged 2 years and older with mild to severe AD. The approval was supported by positive data of the phase 3 ADORING program demonstrating a significant improvement in the vIGA (clear (0) or almost clear (1)) and rapid itch relief (PPNRS at least 4 points reduction) after 8 weeks (ADORING 1&2) and up to 48 weeks (ADORING 3) of treatment in patients who received tapinarof 1% cream compared to those who received vehicle. Tapinarof 1% cream was well-tolerated, the most commonly reported adverse effects reported in ADORING 1&2 were upper and lower respiratory tract infection, folliculitis, headache, asthma, vomiting, ear infection, pain in extremity and abdominal pain[79].

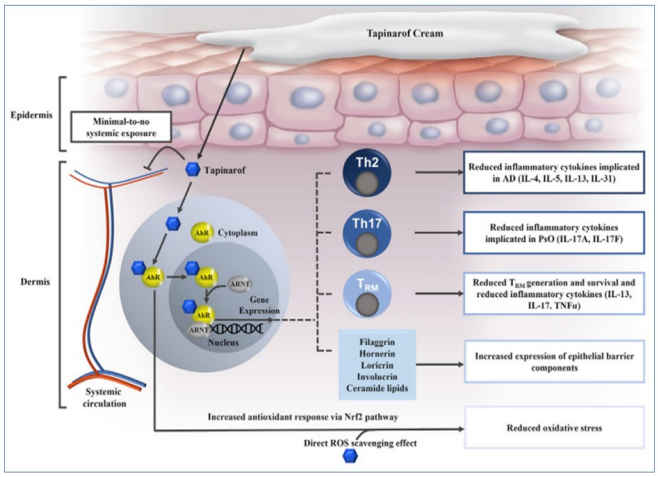


Figure 8: Mechanisms of action of tapinarof in skin diseases[78].

Abbreviations: AD = atopic dermatitis, AhR = aryl hydrocarbon receptor, ARNT = Aryl hydrocarbon receptor nuclear translocator, Nrf2 = nuclear factor erythroid 2–related factor-2, PsO = Psoriasis, ROS = reactive oxygen species, Th2 = Thelper 2 cells, Th17 = Thelper 17 cells, TRM = memory resident T cells[78].

11.1. Current AD drug pipeline

Management of moderate-to-severe AD needs still more effective and safe long-term therapeutic products able to reduce recurrent flares and disease burden. Several new drug developments are emerging including small molecules and biologics tackling old and new targets which should diversify therapeutic options in AD. New innovative approaches are thought to adopt better individual patient needs and requirements including lower dosing frequency and less side effects. The most advanced new drug developments for systemic administration are the monoclonal antibody amlitelimab targeting the OX40/OX40L pathway and the oral TYK2 inhibitor ICP-332. Novel promising topical therapies include ointments of pan-JAK inhibitors including MH004, CGB-500 and LNK01004 and the antimicrobial gel zabalafin.

11.2. Monoclonal antibodies targeting the OX40/OX40L pathway

A new potential therapeutic target in T cell-mediated skin diseases is OX40, a receptor highly expressed on activated T cells and its ligand OX40L (OX40/OX40L), which is mainly expressed on professional antigen-presenting cells (APC) such as Langerhans cells, dendritic cells, B cells, type 2 innate lymphoid cells (ILC2), fibroblasts, endothelial cells and mast cells. Activation of the OX40/OX40L pathway in inflammatory skin enhances effector T cell proliferation and survival, promotes the generation of memory T cells and increases the production of pro-inflammatory cytokines resulting in persistent skin inflammation, chronic itch and skin barrier dysfunction[6]. Blocking OX40/OX40L axis is expected to suppress TH2-driven inflammation, as well as potentially inhibiting TH1, TH17 and TH22 responses. Recent clinical trials investigate the effects of antibodies targeting OX40 (rocatinlimab and telazorlimab) or OX40L (amlitelimab) seeking to demonstrate long-term safety and treatment efficacy in patients with moderate-to-severe AD[80] **(Figure 9)**.

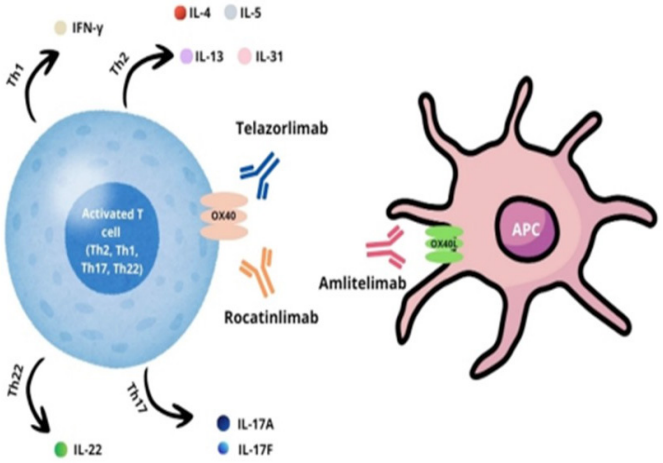


Figure 9: Novel monoclonal antibodies targeting the OX40/OX40L costimulatory signalling pathway[80].

Abbreviations: APC, Antigen-presenting cell; Th, T-helper; IL, interleukin; OX40L, OX40 ligand[80].

Amlitelimab (also known as KY1005 or SAR445229) from Sanofi (licensed from Kymab) is a non-T cell depleting, non-cytotoxic fully human IgG4 monoclonal antibody that blocks the interaction between OX40L on APCs and OX40 on T cells, effectively blocking OX40 stimulation and T-cell-mediated inflammatory responses thereby restoring the balance between pro-inflammatory and regulatory T cells[80]. Positive results from the COAST 1 phase 3 study (NCT06130566) showed that amlitelimab dosed either every 4 weeks or every 12 weeks, met all primary endpoints, demonstrating significant

and clinically meaningful skin clearance and reduced disease severity compared to placebo at week 24 in patients aged 12 years and older with moderate to severe AD. Recently, Sanofi announced that it already plans regulatory filings for AD candidate amlitelimab after reporting positive data in the COAST 2 [NCT06181435) and SHORE (NCT06224348) trials[81]. Phase 3 program is ongoing with trial ESTUARY (NCT06407934) to confirm and extend the findings of COAST 1, COAST 2 and SHORE trials, that blockade of OX40L–OX40 signalling could lead to long-term durable responses with extended dosing frequency beyond every 4 weeks combined with a good safety profile.

Rocatinlimab (previously KHK4083 or AMG 451) from Kyowa Kirin/Amgen is a non-fucosylated IgG1 anti-OX40 monoclonal antibody that inhibits and reduces the number of pathogenic OX40+ T cells[80]. Phase 2b trials showed significant, progressive improvements in clinical severity with a tolerable safety profile in patients with moderate-to-severe AD compared to placebo[82]. Rocatinlimab was tested in the phase 3 ROCKET program with eight trials targeting diverse populations with moderate-to-severe AD, including adults and adolescents with inadequate response, contraindications or intolerance to topical or systemic treatments. A recent safety update from the global ROCKET program identified emerging concerns of malignancies with possible viral or immune-related links. This included one new confirmed case and one suspected case of Kaposi's sarcoma, in addition to the previously confirmed case, suggesting a potential mechanistic link to OX40 pathway modulation. While the overall number of malignancy cases across the program remains below expected background rates, the characteristics of these cases raise a plausible biological concern that cannot be excluded. Based on this update and previously reported safety risks, both Kyowa Kirin and Amgen have concluded that the potential risks may outweigh the benefits for the studied patient populations and discontinued rocatinlimab clinical trials[83].

Telazorlimab (previously ISB830) from Ichnos Sciences is a humanized anti-OX40 IgG1 monoclonal antibody[80]. Telazorlimab has been evaluated in a phase 2b trial (NCT03568162) where it was SC administered at 300mg or 600 mg every 2 weeks in patients with moderate to severe AD. Telazorlimab treatment was well tolerated and the mean percentage change from baseline in EASI was significantly greater in subjects receiving telazorlimab versus placebo at week 16. The most common TEAE were exacerbation of AD, nasopharyngitis, upper respiratory tract infection, viral infection and headache. One patient experienced paraesthesia, considered to be related to telazorlimab treatment and was discontinued from the study[84].

IMG-007 from Inmagene LLC is a non-depleting anti-OX40 monoclonal antibody designed to silence antibody-dependent cellular cytotoxicity (ADCC) function to minimize potential safety risks and to have a prolonged half-life to enable potentially less frequent dosing regimen. Single doses of IMG-007 up to 600 mg were well-tolerated in healthy subjects and exhibited an extended mean terminal half-life up to approximately 38 days at high doses[85]. In the phase 2a open-label trial (NCT05984784) with adult patients with moderate to severe AD, a 4-weeks treatment with IMG-007 resulted in a mean reduction in EASI of 77% and EASI-75 response of 54%, at week 16. Durable inhibition of inflammatory markers including of TH1, TH2 and TH17 cells was observed for up to 24 weeks. IMG-007 infusions were well-tolerated with no reports of pyrexia or chills. The safety and efficacy of various SC dosing regimens of IMG-0047 is currently evaluated in the phase 2b trial (NCT07037901, ADAPTIVE). The primary outcome is the mean percentage change from baseline in EASI at week 20.

11.3. Monoclonal antibodies targeting inflammatory cytokines

APG777 from Apogee Therapeutics is a humanized IgG1 monoclonal antibody with an optimized pharmacokinetic profile. APG777 has high affinity to IL-13 and includes a triple amino acid modification (the "YTE" modification) in its Fc region that is designed to extend its half-life up to 28 days. The dose-proportional systemic exposure of APG777 and positive risk-benefit ratio established in preclinical studies support its continued clinical development for IL-13-mediated diseases. The extended half-life of APG777 suggests potential benefits in reducing dosing frequency compared with existing IL-13-targeting therapies, which could improve treatment adherence and patient outcomes[86]. The safety and efficacy of APG777 are currently being investigated in the Phase 2 clinical trial (NCT06395948) in patients with moderate-to-severe AD; and patients who have already completed treatment will be followed up in the Long-Term Extension (LTE) study (NCT07003425).

Bosakitug (previously ATI-045 or BSI-045B) was in-licensed by Aclaris Therapeutics from Biosion and is a high-affinity humanized anti-thymic stromal lymphopoietin (TSLP) antibody (over 150-fold higher in vitro efficacy compared to tezepelumab) and an extremely low dissociation rate from TSLP leading to long residence time and enhanced neutralization activity and a half-life that can potentially support a dosing interval of every 2 weeks. Aclaris' Chinese partner Chia Tai Tianqing (CTTQ) has already advanced bosakitug into phase 3 trials for severe asthma and chronic rhinosinusitis with nasal polyps.

In the phase 2a Proof-of-Concept (POC) trial (NCT05932654, ADAMANT), 300 mg bosakitug (BSI-045B) SC injections through 23 weeks were able to achieve significant improvements in efficacy measures at week 23 (79% of the AD subjects achieved an IGA 0/1, 89% achieved an EASI-75, 44% achieved an EASI-90 and 28% achieved an EASI-100) and a good safety profile[87]. A further phase 2 trial (NCT07011706) is now investigating the efficacy and safety of repeated SC injections of ATI-045 or placebo administered to approximately 90 adult patients with moderate-to-severe AD. The primary endpoint is percent change from baseline in EASI at week 24. Secondary endpoints at week 24 include EASI50/75/90 responses, vIGA response, BSA response and PP-NRS score, relative to baseline. Top-line results are expected in the second half of 2026.

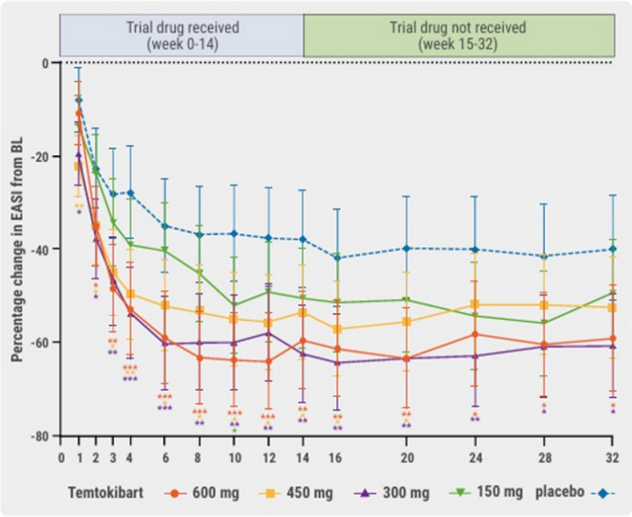
GIA632 from Novartis is a humanized IgG1 monoclonal antibody that selectively binds to interleukin-15 (IL-15) and potently inhibits its activity. IL-15 belongs to the common γ-chain (γc) family of cytokines and is produced by monocytes/macrophages and dendritic cells, as well as by stromal cells in tissues such as epithelium. The target cells for IL-15 are mainly lymphocytes and eosinophils. Intracellular IL-15 signal transduction involves the JAK1/3-STAT3/5 pathway and drives co-stimulatory signals to effector cytotoxic T cells. This way Il-15 promotes tissue protection by the elimination of infected cells. Chronically overexpression of IL-15 in tissues may however trigger the development of T cell-mediated disorders associated with tissue destruction[88]. Although IL-15 is mostly associated

with type 1 (and not type 2) immunity, it has been proposed as a therapeutic target as significant IL-15 overexpression was found in AD skin lesions as well as in AD skin suction blisters[89,90]. A recent genome-wide association study (GWAS) using cell-type enrichment confirmed the known pathobiology of T-cell driven inflammation in AD involving TH1, TH2, TH17 and Treg cell dysregulations[7].

GIA632 is currently investigated in a phase 2a trial (NCT07220577) to assess its efficacy (IGA response at week 16 defined as clear (0) or almost clear (1) score with at least a 2 point-reduction from baseline), safety and tolerability compared to placebo in approximately 84 adult patients with moderate to severe atopic dermatitis.

Galvokimig (UCB9741) from UCB Biopharma is a multi-specific antibody targeting IL-13, IL-17A and IL-17F with an extended half-life through albumin binding. It is designed to selectively inhibit two distinct and separate inflammatory pathways, TH2 (via IL-13) and TH17 pathways (via IL-17A/F), that are involved in the chronic inflammation in AD. Positive data were obtained in a two-part, randomized, first-in-human, proof-of-concept, double-blind Phase 1/2a single dose study of galvokimig, where 47 patients with moderate to severe AD received one intravenous injection of galvokimig (n=33) or placebo (n=14)[91]. At Week 12, a median of 64.9% of patients achieved EASI-75 with galvokimig versus 12.3% with placebo. In addition, a median of 46.6% of patients achieved EASI-90 with galvokimig versus 3.5% with placebo at week 12. In December 2025, the phase 2b dose-ranging trial (NCT07277660) was initiated to investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of galvokimig in adult patients with moderate to severe AD. Participants will receive a predefined galvokimig dose or placebo during initial intervention period. After week 16 participants will continue on the same or a modified dose of galvokimig. The primary endpoint is the EASI-75 at week 16.

Temtokibart (LEO 138559) from LEO Pharma is a monoclonal antibody targeting IL22 receptor subunit alpha 1 (IL22RA1), a receptor for the proinflammatory cytokine IL-22 primarily associated with TH17 and TH22 cell responses. Binding IL22 to the receptor activates JAK1 and TYK2, which further phosphorylate and activate STATs (STAT1, STAT3 or STAT5) which are responsible for a broad spectrum of downstream effects[92]. Increased IL-22 levels are observed in patients with AD and contribute to the manifestation of its characteristic symptoms. Elevated IL-22 levels in patients with AD correlate with increased proliferation of keratinocytes, alterations in the skin microbiota and impaired epidermal barrier function[93,94]. At the EADV 2025 Congress, topline data from the phase 2b trial (NCT05923099) evaluating temtokibart in adults with moderate to severe AD were presented. Temtokibart was well tolerated and significantly reduced EASI scores at week 16 for the 3 highest doses: 300 mg (-64.3%; P < .01), 450 mg (-57.1%; P < .05) and 600 mg (-61.2%; P < .01). The placebo group showed a mean EASI reduction of −41.7%. EASI improvements were generally maintained up to week 32, indicating potentially durable effects of temtokibart in a subset of patients[95] **(Figure 10)**. Temtokibart was well-tolerated with no dose-dependent AEs, low incidence of conjunctivitis and no signal for herpes. In addition, reductions in EASI and SCORAD scores correlated strongly with reductions in TH2, TH17 and TH22 cytokine signatures and improvements in quality-of-life metrics (Dermatology Life Quality Index and Patient-Oriented Eczema Measure)[96].



EASI, Eczema Area and Severity Index; BL, baseline; mg, milligrams.

Figure 10: EASI changes under temtokibart or placebo from baseline to week 16 and up to week 32[95].

12. Regulatory T cell (Treg) Proliferators

Regulatory T cells (Tregs) account for 5-10 % of the peripheral blood CD4+ cells showing the constitutive co-expression of CD25 (also known as the IL-2 receptor alpha). Treg include two main subpopulations: natural Treg (nTreg) expressing the nuclear transcription factor–forkhead winged helix P3 (FoxP3) and inducible Treg which differentiate from nTreg after stimulation with IL-10 (T-regulatory type 1 cells, Tr1) or TGF-ß (Th3/TH2 cells). Treg may express many other receptors including the cytotoxic T lymphocyte-associated protein 4 (CTLA4), the glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR), L-selectin (CD62L) and OX40 (CD134). Due to different expressions of these receptors, Treg modulate the function of other cells not only in the peripheral blood but also in the skin[97,98]. Treg are important modulators of immune responses and able to suppress allergic sensitization and immune responses driven by inflammatory TH1, TH2, TH17 and B cells via several major pathways. In addition, Treg have direct and indirect suppressive effects on mast cells, basophils and eosinophils[99]. Thus, stimulation of Treg proliferation seems to be a promising approach to down-regulate the inflammatory process in skin allergic reaction.

The Treg proliferation stimulator REZPEG (rezpegaldesleukin) from Nektar Therapeutics entered already phase 2 of clinical development for AD. REZPEG is a pegylated-recombinant-human IL-2 that was recently evaluated in the phase 2b REZOLVE-AD trial (NCT06136741) for its efficacy and safety in 393 adult patients with moderate to severe AD. Key enrolment criteria in the study included a minimum EASI score of 16.0, a minimum BSA of 10% and a minimum vIGA-AD of 3. Patients were randomized (3:3:3:2) to receive treatment with three SC doses of REZPEG (a high dose of 24 µg/kg every two weeks, a middle dose of 18 µg/kg every two weeks and a low dose of 24 µg/kg every four weeks or placebo every two weeks). The trial met its primary endpoint of the mean improvement in Eczema Area and Severity Score (EASI) from baseline at week 16 for all three dose arms of REZPEG versus placebo (p<0.001). All three dose arms also achieved statistical significance at week 16 for the key secondary endpoints of EASI-75, EASI-50 and BSA[100] **(Table 5)**. In addition, blood biomarker data demonstrate

on-target and dose-dependent pharmacological activity with an increase in total Tregs of up to 6-fold in the high dose arm. Sustained Treg cell proliferation was observed at week 16 as compared to baseline and was correlated with reduction of key TH2 inflammatory markers: IL-19, TARC (Thymus and activation-regulated chemokine - also known as CCL17), periostin and MDC/CCL22.

Table 5: Primary endpoint and key secondary endpoint data of the phase 2b REZOLVE-AD trial[100].

	REZPEG 24 µg/kg q2w (high dose)	**REZPEG 18 µg/kg q2w (middle dose)**	**REZPEG 24 µg/kg q4w (low dose)**	**Placebo**
Primary Endpoint	N=104	N=106	N=110	N=73
Mean improvement in EASI score from baseline	61% p<0.001	58% p<0.001	53% p<0.001	31 %
KeySecondary Endpoints				
EASI-75	42% p<0.001	46% p<0.001	34% p<0.05	17 %
EASI-50	66% p<0.001	66% p<0.001	55% p<0.01	34 %
Mean improvement in BSA score from baseline	54% p<0.001	48% p<0.001	43% p<0.001	17 %
vIGA-AD 0/1	20% p<0.05	26% p<0.01	19% ns	8 %
EASI-90	25% p<0.05	18% ns	17% ns	9 %
*Itch NRS**	42% *p<0.01*	35% *p<0.05*	23% *ns*	16 %

*Patients with baseline Itch NRS ≥ 4 used as denominator for assessing Itch NRS response (N=63, 95, 92 and 102 for the placebo, 24 µg/kg q2w, 18 µg/kg q2w and 24 µg/kg q4w arms); ns=not significant[100].

13. Kinase Inhibitors

ICP-332 from Beijing InnoCare Pharma is an oral highly potent and selective TYK2 inhibitor. By acting on the TYK2 kinase domain (JH1), ICP-332 inhibits the activity of inflammatory cytokines, such as IL-23, IL-12, IFN-α and IFN-β and thereby, it inhibits pathways involved in the pathogenesis of AD. ICP-332 has already entered phase 3 (NCT06775860) of clinical development due to the positive phase 2 results in patients with moderate to severe AD, in which once daily doses of ICP-332 80 mg or 120 mg compared to placebo resulted in significant reductions in EASI scores from baseline to week 4 combined with a good safety profile[101].

Soquelitinib (CPI-818) from Corvus Therapeutics is an oral selective inhibitor of IL-2 inducible T cell kinase (ITK), an enzyme that is expressed predominantly in T cells and plays a role in T cell activation and differentiation. Soquelitinib has been shown to induce the generation of Th1 helper cells while blocking the development of both Th2 and Th17 cells and production of their secreted cytokines. Th2 and Th17 helper T cells are involved in the pathogenesis of many autoimmune and allergic diseases including AD. In addition, soquelitinib has demonstrated anti-tumor activity in vivo in several syngeneic murine tumor models and may represent a novel approach to cancer immunotherapy[102]. Soquelitinib has already demonstrated positive safety and efficacy results in a phase 1 trial (NCT06345404) in moderate to severe AD patients, who have received prior systemic therapy including patients who were treatment resistant[103]. Based on these data, a first phase 2 trial (NCT07441395) is currently evaluating soquelitinib in patients with moderate to severe atopic dermatitis that have failed at least one prior topical or systemic therapy. Furthermore, due to positive results of a phase 1b clinical trial in patients with refractory T cell lymphomas, which demonstrated tumor responses in very advanced, refractory, difficult to treat T cell malignancies, a phase 3 registration trial (NCT06561048) investigates the safety and efficacy of soquelitinib in patients with relapsed/refractory peripheral T cell lymphoma.

ATI-2138 from Aclaris Therapeutics is an oral dual inhibitor of the IL-2 inducible T cell kinase (ITK) and JAK3 blocking T cell activation and proinflammatory cytokine signalling in atopic skin. ITK regulates T cell receptor signal transduction and inhibition of this kinase can affect T cell differentiation and activation. JAK3 is a key signal transduction kinase that forms a heterodimer with JAK1, modulates JAK1 phosphorylation of STAT5 and regulates cytokines that signal through the IL-2 receptor common gamma chain (IL-2Ɣc) to affect lymphocyte proliferation and activation. A small phase 2a open-label clinical trial (NCT06585202) investigated ATI-2138 administered over 12 weeks to participants with moderate to severe AD. Twelve patients completed the study and data from 9 per protocol patients were evaluated. The trial has demonstrated potential AT-2138 efficacy (77.1 % mean improvement in EASI score at week 12). About 62.5 % of patients experienced at least a 4-point improvement of the PPNRS. The safety profile was good (no severe adverse events). Pharmacodynamic analyses demonstrated modulation of both the ITK and JAK3 pathways. Near-complete (~95%) ITK target occupancy was observed at peak, with 60-70% persisting at trough. Immunophenotyping of whole blood showed no significant perturbation in T cells or NK cells. Proteome and transcriptome tape strip and biopsy analyses of lesioned skin showed significant reduction of multiple inflammatory markers with downregulation of key ITK-dependent pathways (Th2, Th17, TCR and T-cell activation), along with reduction in fibrosis-related markers and changes in epidermal barrier genes suggesting restoration of skin homeostasis. Nevertheless, the current dose of 10 mg was considered low, suggesting higher doses may be needed in a larger phase 2 trial[104,105].

Barzolvolimab (CDX-0159) from Celldex Therapeutics is a humanized IgG1κ monoclonal antibody that binds the extracellular domain of the receptor tyrosine kinase KIT (c-KIT/CD117) with high specificity and sub-nanomolar affinity and allosterically inhibits activation by its only ligand Stem Cell Factor (SCF). Modifications to the Fc fragment of barzolvolimab eliminated FcγR binding and the potential for significant infusion-related reactions through Fc-mediated mast cell activation and enhanced antibody serum exposure in non-human primates. KIT is highly expressed in mast cells, which are important immune sentinel cells but increased mast cell activity is involved in allergies, inflammation and pruritus, the key drivers of AD.

Inhibition of KIT/SCF by barzolvolimab reduces mast cell differentiation, maturation and survival. Barzolvolimab has shown a good safety profile and target-engagement through suppression of plasma tryptase (a marker of tissue mast cell numbers) in healthy human subjects supporting its potential utility in mast cell-driven disorders[106]. Barzolvolimab is currently tested in a phase 2 trial (NCT06727552) in patients with moderate to severe AD will receive barzolvolimab by SC injections of 150 mg or 300 mg (after an initial loading dose of 450 mg) or placebo every 4 weeks followed by a re-randomized crossover treatment regimen for further 16 weeks. The primary endpoint is the percent change from Baseline in the weekly average of the daily worst-itch (PP-NRS) score at Week 16.

CGB-500 (ointment of tofacitinib) from CAGE Bio is a novel ionic liquid–based topical therapy of the pan-JAK inhibitor tofacitinib in development for patients with atopic dermatitis. In 2025, positive results from a phase 2b dose-ranging study of CGB-500 (NCT06810050) have been announced demonstrating efficacy, rapid itch relief and a favourable safety profile in AD patients with moderate to severe disease affecting less than 10% of BSA[107]. Approximately 59% of patients achieved clear or almost clear skin with at least a two-grade improvement of IGA and 71% of patients achieved at least a 4-point reduction on the PP-NRS scale. About 35% of patients reported a “0” itch score, indicating complete resolution of itch symptoms. CGB-500 was generally well tolerated with no new or unexpected safety concerns identified in the trial.

MH004 (tofacitinib etocomil) 1.0% ointment from Minghui Pharmaceutical is a twice-daily pan-Jak inhibitor, for which positive results were obtained in a phase 3 trial (NCT07185282) in adolescents (ages 12 years and older) and adults with mild to moderate AD. Both primary endpoints (IGA of clear or almost clear with a 2-grade improvement and EASI75) were met at week 4: 41.0% of individuals treated with MH004 1.0% achieved IGA-TS compared to 10.3% treated with vehicle (P<0.0001 and 58.2% of individuals treated with MH004 1.0% achieving EASI-75 compared to 19.8% treated with vehicle (P<0.0001). Additionally, the key secondary endpoints, including IGA-TS and EASI-75 at week 8, as well as the proportion of participants with a ≥ 4-point improvement in Itch Numerical Rating Scale (NRS4) score at week 8, were met. MH004 1.0% was safe and well-tolerated[108].

LNK01004 from LYNK Pharmaceuticals is a topical pan-JAK inhibitor, showed significant efficacy in treating moderate-to-severe atopic dermatitis in a phase 2 trial (NCT07071610)[109]. At week 8, both concentrations of LNK01004 demonstrated superior efficacy compared with vehicle, with the most pronounced responses observed in patients with higher baseline BSA involvement. Among patients with BSA ≥10%, EASI-75 response rates were 61.1% for the 0.3% group and 46.2% for the 1.0% group, compared with 20% for vehicle. Similarly, vIGA-AD response rates (0/1 with ≥2-point improvement) were 44.4% and 38.5% for the 0.3% and 1.0% groups, respectively, versus 10% for vehicle. LNK01004 was well tolerated, with no treatment-related serious adverse events reported. All treatment-related adverse events were mild or moderate (Grade 1–2). Pharmacokinetic analyses revealed low systemic exposure, with mean Cmax values of 0.06 ng/mL for the 0.3% dose and 0.15 ng/mL for the 1.0% dose.

14. STAT 6 Degrader

Targeting STAT6 directly may represent a new approach to therapeutically modulate JAK–STAT signalling in AD and related allergic conditions[110,111]. STAT6 (Signal Transducer and Activator of Transcription 6) is an essential transcription factor in the IL-4 and IL-13 signalling pathways and the central driver of TH2 immune responses, including IgE class switching, eosinophil recruitment, mucus production and expression of inflammatory mediators such as eotaxin (CCL11) and TARC (CCL17)[112]. Multiple gain of function mutations of STAT6 were identified to cause severe allergic diseases in humans[113]. Dupilumab, an injectable monoclonal antibody that blocks IL-4/13 signalling, is an approved therapy for multiple allergic diseases. STAT6 targeting is therefore supported by both human genetics and dupilumab’s clinical pathway validation[114].

KT-621 from Kymera Therapeutics is a first-in-class highly potent oral STAT6 degrader that can selectively degrade and deplete STAT6 in various disease relevant human immune and tissue cells, fully block various IL-4/13 functions in these cells with picomolar IC50 lower than the IL-4Rα monoclonal antibody dupilumab and does not degrade or inhibit any other STAT transcription factors. In a MC903-induced atopic dermatitis mouse model orally administered KT-621 demonstrated complete inhibition on the total serum IgE, a TH2 inflammation biomarker[114] **(Figure 11)**. In the phase 1b BROADEN trial (NCT06945458), KT-621 (100 mg and 200 mg once daily oral treatment for 28 days) showed significant STAT6 degradation in blood and skin, indicating effective target engagement in AD patients. In addition, a reduction in type 2 inflammatory biomarkers (similar to IL4/IL-13 blockage) and relevant improvements on clinical endpoints (EASI-75 improvement from baseline was 33% and 25% in the 100 mg and 200 mg dose groups, respectively) and patient-reported outcomes were reported which need to be confirmed in larger trials. KT-621 was reported to be well tolerated with no unexpected safety issues or dose-limiting toxicities reported, though detailed adverse event data have not yet been released[115]. KT-621 is currently in Phase 2 clinical testing - a Phase 2 BROADEN2 trial (NCT07217015) started in November 2025 in moderate to severe AD patients with data expected to be reported by mid-2027. It is a 16-week double-blind, placebo-controlled study with a 52-week open-label period and intended to enable dose selection for subsequent parallel phase 3 trials in AD.

15. Other

Zabalafin hydrogel from Alphyn Biologics is a non-steroidal, topical AD treatment containing multiple bioactive (undisclosed) components which are directly targeting the bacteria living

on the skin of patients with AD. Bacteria like Staphylococcus aureus naturally live on the skin and discharge toxins that make AD symptoms worse and often cause infection and prevent healing. In a phase 2a trial, about 90% of patients experienced a 1-point reduction in IGA score and a Patient Oriented Eczema Measure (POEMA) scale quality-of-life improvement of at least 6 by the end of treatment with zabalafin 9.5% gel. Additionally, 68% of patients experienced an itch score improvement of at least 4 on the PP-NRS with 84% of patients with infected skin reaching complete clearance. All patients also had a decrease in Skin Infection Rating Scale (SIRS) score with only 1 reported treatment-emergent adverse event of mild transient stinging[116]. A phase 2b trial (NCT06855745, CLEAR-AD1) is currently testing the efficacy, safety and tolerability of a 9.5 % zabalafin gel compared to vehicle for 4 months in 72 patients with mild to moderate AD.

Based on a thorough review of the clinical trial projects currently in phase 2 and phase 3 published on CLINICALTRIALS. GOV and the publicly available literature, the current drug candidates for topical and systemic administration are summarised in **(Table 6 and Table 7)**, respectively.

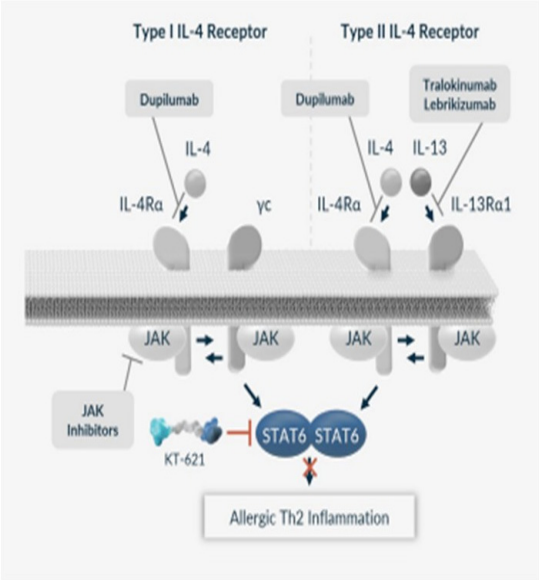


Figure 11: KT-321 inhibits IL-4 and IL-13 signalling pathways and Th2 Inflammation in AD[114].

Table 6: Currently most advanced AD drug candidates for topical administration.

Product / Sponsor	Target/ Route of administration	Development Phase/NTC (clinialtrials.gov)
JAK Inhibitors		
MH004 (tofacitinib etocomil) / Minghui Pharmaceutical	Novel 1% ointment of tofacitinib	Phase 3: NCT07185282 Completed in AUG-2025
CGB-500 / CAGE Bio	Novel ionic liquid–based ointment of tofacitinib	Phase 2b: NCT06810050 Completed 2025, positive results announced SEP-2025
LNK01004 / LYNK Pharmac.	Topical pan-JAK inhibitor	Phase 2 trial: NCT07071610 Completed 2025, positive results announced NOV-2025
Other		
Zabalafin gel / Alphyn Biologics	Multiple bioactive components targeting bacteria living on AD skin	Phase 2: NCT06855745 (CLEAR-AD1) Recruiting, SCE: NOV-2025
Abbreviations: JAK = Janus kinase, SCE = Study completion estimated		

Source: Data in public domain on ClinicalTrials.gov

Table 7: Currently most advanced AD drug candidates for systemic administration.

Product / Sponsor	Target/ Route of administration	Development Phase/NTC (clinialtrials.gov)
Monoclonal antibodies targeting inflammatory cytokine signalling		
APG 777 / Apogee Therapeutics	High-affinity anti-IL-13 mAb with extended half-life for SC injection	Phase 2: NCT06395948 Recruiting, SCE: JUN-2028 NCT07003425 (LTE of NCT06395948), Recruiting, SCE: DEC-2029
Bosakitug (ATI-045, previously BSI-045B) / Aclaris Therapeutics	High-affinity humanized anti-TSLP antibody (over 150-fold higher in vitro efficacy compared to Tezepelumab) for SC injection	Phase 2: NCT07011706 Active, Not Recruiting, SCE: OCT-2026
GIA632/ Novartis	Humanised anti-IL15 mAb for SC administration	Phase 2a: NCT07220577 Recruiting, SCE: Sep 2027
Galvokimig (UCB9741) / UCB Biopharma	Bispecific antibody targeting IL-13, IL-17A, IL-17F for IV and SC injection	Phase 2: NCT07277660 Recruiting, SCE: MAR-2028
Temtokibart (LEO 138559) / LEO Pharma	Anti-IL-22 mAb	Phase 2b: NCT05923099
Monoclonal antibodies targeting OX40/OX40L pathway		
Amlitelimab (SAR445229) / Sanofi	Fully human anti-OX40L IgG4 mAb for SC administration	Phase 3: ESTUARY (NCT06407934) Ongoing to confirm and extend the findings of COAST 1 (NCT06130566), COAST 2 (NCT06181435) and SHORE (NCT06224348)
Telazorlimab (ISB 830) / Ichnos Sciences SA	Humanized anti-OX40 IgG1 for SC administration	Phase 2b: NCT03568162 Completed AUG 2021
IMG-007 / Inmagene LLC	anti-OX40 mAb engineered to silence ADCC function for SC injection	Phase 2b: NCT07037901 (ADAPTIVE) Recruiting, SCE: OCT-2027

Product / Sponsor	Target/ Route of administration	Development Phase/NTC (clinialtrials.gov)
Treg proliferators		
REZPEG (rezpegaldesleukin)/ Nektar Therapeutics	Pegylated-recombinant-human IL-2 for SC administration	Phase 2b: NCT06136741 (REZOLVE-AD) Long-term maintenance phase ongoing
Kinase Inhibitors		
ICP-332 / Beijing InnoCare Pharma	Oral TYK2 inhibitor	Phase 3: NCT06775860 Recruiting, SCE: DEC-2026
ATI-2138 / Aclaris Therapeutics	Oral dual inhibitor of ITK and JAK3	Phase 2: NCT06585202Completed MAR-2025
Barzolvolimab (CDX-0159) / Celldex Therapeutics	Humanized anti- KIT mAb for SC administration	Phase 2: NCT06727552 Recruiting, SCE: May-2027
Soquelitinib (CPI-818) / Corvus Pharmaceuticals	Oral ITK inhibitor	Phase 2: NCT07441395 Recruiting, SCE: SEP-2027
STAT 6 Degrader		
KT-621 / Kymera Thrapeutics	Oral STAT 6 degrader	Phase 2: NCT07217015 Recruiting, SCE JUN-2028
Abbreviations: ADCC = antibody-dependent cellular cytotoxicity, AhR = aryl hydrocarbon receptor, ITK = IL-2 inducible T cell kinase, JAK = Janus kinase, KIT = CD117, LTE = long-term-extension; mAb = monoclonal antibody, SC = subcutaneous, SCE = Study completion estimated, SYK = Spleen tyrosine kinase, TYK2 = Tyrosine kinase 2.		

Source: Data in public domain on ClinicalTrials.gov

16. Concluding Remarks

Managing atopic dermatitis is complex and often faces challenges such as treatment resistance, medication adherence or identifying triggers. Individual therapy needs to be tailored to patient needs and disease severity. The ideal outcome in AD patients would be no itch, no rash and no adverse effects. A big step in this direction was the approval of monoclonal antibodies targeting TH2 immune responses such as dupilumab, tralokinumab, lebrikizumab and recently also nemolizumab. This has encouraged the development of small compounds targeting the TH2 interleukin IL-4/IL-13 pathway, such as JAK inhibitors, which can be taken orally and work fast to relieve symptoms, particularly itching. Unlike monoclonal antibodies that target only one or two specific cytokines, JAK-inhibitors block multiple signalling pathways at once, making them highly effective against a wide range of inflammatory signals in AD. This comprehensive blockade, however, can affect essential immune functions, which may lead to side effects like an increased risk of severe infection. In addition, FDA still requires black box warnings about an increased risk of serious heart-related events, cancer, blood clots and death for the class of JAK inhibitors. In this regard, long-term comparative efficacy and safety data are still missing in the literature. Some new topical therapies have recently reached the US and Japanese market including novel JAK inhibitors (ruxolitinib, delgocitinib), phosphodiesterase 4 (PDE4) inhibitors (crisaborole, difamilast, roflumilast) and the aryl hydrocarbon receptor agonist tapinarof. New innovative approaches for systemic therapy are thought to adopt better individual patient needs and requirements including lower dosing frequency and less side effects. Most advanced new drug developments are monoclonal antibodies targeting the OX40/OX40L pathway, such as amlitelimab and the oral TYK2 inhibitor ICP-332 for systemic administration. Novel promising topical therapies include ointments of pan-JAK inhibitors, such as MH004, CGB-500 and LNK01004 and the antimicrobial gel zabalafin.

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