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Review Article

Comparative Effectiveness and Safety of Novel Topical Agents for Atopic Dermatitis in the Adult Population: A Literature Review

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Abstract

Atopic Dermatitis (AD) is a chronic skin condition marked by itching, erythema and skin barrier dysfunction, affecting millions globally and significantly impacting quality of life of patients. Current therapies, such as topical corticosteroids and calcineurin inhibitors, while effective, present safety concerns, especially with their prolonged use. The development of novel topical agents targeting specific inflammatory pathways has emerged as a promising approach for AD management, addressing both the efficacy and safety limitations of more established treatments. Among these new therapies, Phosphodiesterase-4 (PDE-4) inhibitors like crisaborole and roflumilast and Janus Kinase (JAK) inhibitors like ruxolitinib and delgocitinib show considerable efficacy and favourable safety profiles in reducing AD symptoms and improving skin barrier function. Additionally, innovative agents like tapinarof an Aryl hydrocarbon Receptor (AhR) modulator and asivatrep, a TRPV1 antagonist, demonstrate potential in improving AD symptoms with research also exploring the therapeutic role of skin microbiome modulation through topical probiotics.

This research synthesizes findings from randomized controlled trials, meta-analyses and observational studies to evaluate the comparative effectiveness and safety of these newer topical agents with the aim of providing insights into optimal management strategies for mild-to-moderate AD in adults. Such evidence is crucial to guide clinical decision-making, improve patient outcomes and enhance therapeutic options in AD care.

Keywords: Atopic Dermatitis; Novel Topical Treatments; Adults; Mild-To-Moderate; Review

Introduction

Atopic Dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritus, erythema, immune dysregulation and barrier dysfunction [1]. This condition significantly impacts patients' quality of life by causing physical discomfort and psychological stress. Its relapsing nature and flares impose a substantial burden on individuals and healthcare systems worldwide, underscoring the need for effective and safe therapies [2]. It affects 15-20% of children and 1-3% of adults globally, emphasizing the urgency for optimized treatments to mitigate symptoms and address disease pathology [3-5].

Recent advances in AD pathophysiology facilitated the development of topical agents targeting specific inflammatory pathways. PDE-4 inhibitors, such as crisaborole, reduce inflammation by modulating cyclic Adenosine Monophosphate (cAMP), a signaling molecule central to immune activation [6]. Clinical trials confirm its efficacy in symptom reduction and long-term safety [7]. Similarly, JAK inhibitors like ruxolitinib block the JAK-STAT pathway, a critical mediator of cytokine signaling in AD, showing significant improvements in inflammation and skin barrier function with favorable safety profiles [8,9]. Emerging therapies offer additional promise. Tapinarof an Aryl hydrocarbon Receptor (AhR) modulator, has demonstrated efficacy in improving symptoms and barrier function. TRPV1 antagonists, such as asivatrep, are being investigated for their ability to alleviate pruritus and inflammation [11]. Furthermore, efforts to restore natural skin microbiota with topical probiotics have shown potential to

enhance barrier integrity and immune regulation [12,13].
As the understanding of AD's pathogenesis evolves, so does the development of more directed treatments. These innovations aim to address current unmet needs in AD, particularly in improving the tolerability and safety profiles of available therapies. Given the chronic nature of the disease and associated treatment challenges, the introduction of these novel therapies represents a significant advancement in the field.

Methodology
An extensive literature review was performed between July and November 2024 using primarily PubMed, Medscape, Google Scholar, Cochrane Library and ClinicalTrials.gov. Keywords included: "atopic dermatitis" OR "eczema" AND "mild-to-moderate" AND "tapinarof" OR "ruxolitinib" OR "roflumilast" OR "delgocitinib" OR "brepocitinib" OR "lepzacitinib" OR "tofacitinib" OR "jaktinib" OR "ivarmacetinib" OR "lfidancitinib" OR "crisaborole" OR "difamilast" OR "lotamilast" OR "asivatrep" OR "niclosamide" OR "ATx201" OR "new topical agents" OR "novel treatments" OR "JAK inhibitors" OR "PDE-4 inhibitors" OR "aryl hydrocarbon receptor agonists" AND "efficacy" OR "effectiveness" OR "safety" AND "IGA" "EASI" OR "SCORAD" OR "NRS" OR "patient-reported outcomes." The search was limited to peer-reviewed articles published within the last eight years to ensure the most recent data was considered. Moreover, only trials involving adult patients with mild-to-moderate AD were included to focus on the target population.

Inclusion criteria encompassed studies involving adult patients with mild-to-moderate AD, newer topical agents, Randomized Controlled Trials (RCTs) at least in Phase 2 and systematic reviews/meta-analyses. Studies had to report efficacy and/or safety endpoints, including EASI, IGA, SCORAD, adverse events and patient-reported outcomes. Exclusion criteria included trials focusing solely on mild or severe AD, other eczematous conditions, pediatric populations, systemic therapies and non-randomized clinical trials. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used to ensure a systematic, transparent and replicable process for conducting a comprehensive literature review on the comparative effectiveness of novel topical agents for atopic dermatitis in adults, guiding the selection process from identification, screening and eligibility assessment to final inclusion.

Initially, abstracts were screened to determine eligibility. If sufficient information could not be obtained through the abstract, the full text was reviewed. Eligible studies would undergo a full-text review and those meeting the inclusion criteria were included in the final review. Data extraction involved systematically collecting information on study characteristics, including author, year of publication, AD severity, design, study duration, sample size, patient demographics, treatment protocols or drugs utilized (including the dose), outcome measures (such as EASI, IGA, itch NRS) and reported AEs. The extracted data was organized into a standardized spreadsheet in Microsoft® Excel® for comparison.

In total, 187 studies were identified as potentially significant to address the research topic. Out of these studies, 43 were excluded as they were duplicates. Another 31 studies were removed due to being exclusively in paediatric populations. Additionally, 25 studies were excluded since they involved non-topical therapies and 32 publications were removed as they were non-randomized clinical studies. This resulted in 56 included studies for the analysis. The findings were summarized, providing an overview of the study designs, population demographics, interventions and outcomes of the included trials.

Results
In AD, most mild to moderate patients are managed by topical therapy with TCSs and TCIs being the preferred first line treatment for decades. However, better molecular understanding of the pathophysiology of atopic dermatitis have led to the discovery of relevant targets, resulting in new agents that target specific cytokines or receptors, restoring skin barrier integrity and reducing inflammation, without the traditional AEs commonly linked to conventional therapies. This chapter will explore the recent advancements for those novel topical therapies, that are either in clinical development or recently approved for adults with mild to moderate AD.

Aryl Hydrocarbon Receptor Agonists
The aryl hydrocarbon receptor was first identified as an intracellular protein that mediated the toxic effects of dioxin, being part of the Pern-Arnt-Sim (PAS) superfamily of transcription factors, involved in many biological activities. After its activation, AhR translocates from the cytoplasm to the nucleus, modulating the transcription of target genes [14].

AhR is vastly expressed in the skin and is involved in the regulation of genes related to the skin barrier, such as filaggrin, involucrin and loricrin, promoting epidermal barrier differentiation. Accordingly, AhR plays a vital role in the development and maintenance of the epidermal homeostasis and response to environmental factors, like UVA, UVB, allergens or bacterial products, for instance [15,16].

Tapinarof

Tapinarof is the first specific AhR, naturally obtained as a bacterial (Photorhabdus luminescens) byproduct. It regulates the expression of proteins related to the epidermal barrier and supresses key cytokines implicated in the disease pathobiology [16].

Its randomized, double blinded, phase 3 pivotal clinical trials (NCT05014568 and NCT05032859) investigated the efficacy and safety of tapinarof cream 1% in 813 patients with AD. Additionally, there is also an ongoing Phase 3 open label extension (NCT05142774) which will evaluate the safety and efficacy of topical tapinarof cream 1% in subjects with atopic dermatitis.

After 8 weeks of treatment, approximately 46-47% of patients achieved a "clear" or "almost clear" skin response (validated investigator global assessment for atopic dermatitis - vIGA-AD 0/1) with at least a 2-grade improvement compared to 13.9-18% in the vehicle group. Regarding Eczema Area and Severity Index (EASI) 75, 56-59% of subjects achieved the endpoint in the active arm, against 21-22% for vehicle. The cream provided itch relief with at least a 4-point reduction in the average weekly Peak Pruritus Numerical Rating Scale (PP-NRS) in 52.8-55.8% patients, versus 24.1-34.2% in vehicle [10].

Tapinarof cream was generally well-tolerated across the studies with most Treatment-Emergent Adverse Events (TEAEs) being mild to moderate in severity and with low discontinuation rates. There were rare serious AEs and none related to treatment. Notably, discontinuation rates due to AEs were lower for patients in the active arm compared to vehicle, respectively 1.5-1.9% vs.3-3.6%. The most common AEs (>5%) were folliculitis, headache and nasopharyngitis. The incidence of contact dermatitis was also lower in both trials for patients treated with tapinarof compared to those receiving vehicle: 1.1-1.5% vs.1.5-2.2%. All cases of contact dermatitis were mild to moderate, leading to few discontinuations from trial or treatment and without any severe events. The findings from the trials demonstrate consistent effectiveness results with tapinarof outperforming the vehicle in multiple endpoints with therapeutic potential across different AD populations, like for those patients where TCS are inadvisable. The safety profile of tapinarof is also reassuring with AEs being predominantly mild to moderate, including folliculitis, headache and nasopharyngitis. Remarkably, the incidence of serious AEs was low and unrelated to the study drug and discontinuation rates due to AEs were also lower in the active arm (1.5-1.9%) compared to the vehicle (3-3.6%). While the data suggest that tapinarof is an effective and well-tolerated treatment for AD, some gaps in the literature would prompt further considerations. One of those being the long-term safety of tapinarof, as the Phase 3 open-label extension (NCT05142774) is still ongoing. Additionally, while tapinarof has been shown to outperform placebo in reducing symptoms of AD, further head-to-head studies comparing its effectiveness against other established treatments, such as corticosteroids or calcineurin inhibitors, could provide a more comprehensive benefit-risk analysis.

The current trials focus on a relatively short treatment duration (8 weeks), so examining how efficacy evolves after extended treatment periods is important for assessing its role in chronic AD management. Lastly, further exploration into the specific mechanisms of AhR could potentially expand its applicability to other dermatological diseases or subpopulations of AD.

Janus Kinase Inhibitors (JAKi)

JAKs are intracellular tyrosine kinases named for their tandem architecture, resembling the Roman god Janus [17]. The JAK family includes JAK1, JAK2, JAK3 and TYK2, which, together with STAT proteins, activate the JAK-STAT pathway upon cytokine, growth hormone, colony-stimulating factor or interleukin binding. This pathway regulates cell proliferation, survival and differentiation, particularly in immune and hematopoietic systems. In AD, JAK-STAT activation drives Th2-heavily skewed inflammation, suppresses regulatory T-cells, activates eosinophils and increases secretion of pro-inflammatory cytokines [16,18].

Ruxolitinib

Ruxolitinib is a JAK 1/2 inhibitor (JAKi) and its systemic version was the first approved JAK (for myeloproliferative disorders). The topical formulation of ruxolitinib received FDA approval a few years later, in 2021, for the short-term and non-continuous chronic treatment of mild-to-moderate AD in non-immunocompromised patients whose disease is not well controlled. Its

efficacy and safety were demonstrated by two pivotal, phase 3 trials, Topical Ruxolitinib Evaluation in Atopic Dermatitis (TRuE-AD) 1 and 2.

TRuE-AD 1 and 2 randomized more than 600 patients each, in a 2:2:1 ratio to receive either 0.75% cream, 1.5% cream or vehicle twice daily for the initial 8 weeks. Key inclusion criteria included patients aged 12 years or older, a diagnosis of AD for at least 2 years an Investigator's Global Assessment (IGA) score of 2-3 and body surface area (BSA) involvement of 3-20%. After those 8 weeks, eligible patients could maintain treatment for another 44 weeks with either 0.75% or 1.5% cream with vehicle being re-randomized to one of the active arms.

The primary endpoint an IGA score of 0-1 at week 8, was met by 50% and 39% of patients in TRuE-AD 1 and TRuE-AD 2, respectively, for the 0.75% cream. When looking into the 1.5% cream, the figures were 53.8% and 51.3%, compared to 15.1% and 7.6% for the vehicle ($p < 0.0001$). Additionally, EASI-75 at week 8 was achieved by 56.0% and 51.5% of patients on the 0.75% cream, 62.1% and 61.8% on the 1.5% cream and 24.6% and 14.4% on the vehicle, respectively. Significant improvements were also observed in EASI-90 and Numerical Rating Scale (NRS) scores ($p < 0.05$). Notably an improvement in itch was reported as early as 12 hours after starting the 1.5% cream [9].

The most common TEAE was an application site burning sensation, interestingly more observed with vehicle (4.4%) than with the 0.75% (0.6%) or 1.5% (0.8%) creams. There were no serious AEs reported. During the 52 weeks long-term safety, patients only had to treat active areas and discontinue treatment three days after lesion clearance, resuming at the first sign of recurrence.

The proportion of patients from weeks 8 to 52 with an IGA score 0/1 (clear or almost clear) with ruxolitinib 0.75% and 1.5% creams ranged from 62.4%-76.9% and from 66.5%-77.3%, respectively, in TRuE-AD 1 and from 59.6%-76.7% and from 72.0%-80.1% in TRuE-AD 2. Throughout the period, the mean total BSA remained below 3% for patients using the 1.5% cream and for most of the time for the 0.75% cream. TEAEs for the 0.75% and 1.5% creams were reported in 60.1% and 53.8% of patients and related AEs to treatment were reported in 20 patients (4.7%) using the 0.75% cream and in 13 patients (2.9%) using the 1.5% cream, without any serious reports. The most frequent AEs included nasopharyngitis, upper respiratory infections and influenza.

TEAEs led to discontinuation in nine patients (2.1%) in the 0.75% cream group with no discontinuations in the 1.5% cream group. In summary, approximately 70% of patients maintained their clear or almost clear status (IGA score 0/1). Ruxolitinib cream was well tolerated in the long-term setting with no serious treatment-related AEs [16].

The trials offered robust evidence of the efficacy and safety of ruxolitinib, particularly with long-term results showing sustained improvements in IGA scores and diminished BSA involvement. Another interesting feature was the rapid pruritus relief, something quite beneficial for patients. A limitation for the studies was that severe patients were excluded, as with many topicals, something that can restrict the reproducibility of the trials in the general population. In addition, there are no direct comparative studies between ruxolitinib and other topical treatments for AD, so the comparison against other molecules is difficult. Lastly, exploring its potential for continuous treatment versus intermittent use could provide valuable insights into optimizing the long-term management of AD.

Delgocitinib

Delgocitinib was the first topical JAK to be approved for AD in 2020. It is a topical pan-JAKi that targets JAK1, JAK2, JAK3 and TYK2, modulating the activity of different immune cells (B and T lymphocytes, monocytes and masT-cells) and promoting restoration of the epidermal barrier [16,19]. Currently, there are two distinct formulations of delgocitinib an ointment, mainly used in Japan and the only one approved for atopic dermatitis and the cream, which is still under phase 2 of clinical development for AD.

The pivotal phase-3 RCTs evaluating delgocitinib ointment for AD in adults were QBA4-1 and QBA4-2. QBA4-1 was a 2-part study, initially with a 4-week, randomized, double blinded, vehicle-controlled period (part 1), followed by a 24-week open label extension as part 2, on which all subjects received the drug. QBA4-1 recruited Japanese patients > 16 years-old with a modified EASI (mEASI) score above 10, IGA of 3/4 and BSA of 10%-30%. Those in part 1 who experienced worsening of AD could either discontinue treatment or move into part 2, as per investigator decision [16].

During Part 1, the percentage changes from baseline in mEASI scores were -44.3% in the active group compared to 1.7% in the vehicle after 4 weeks ($P < 0.001$), also with improvements in the pruritus NRS ($p<0.01$). Furthermore, more subjects in the active arm reached mEASI-50 (51.9% vs 11.5%) and mEASI-75 (26.4% vs 5.8%). In part 2, all the assessments kept improving throughout the 24 weeks with the change from baseline in mEASI being -56.3%, 69.3% achieving mEASI-50 and 35.8% reaching mEASI-75. QBA4-2 was a 52-week, open-label, multi-site, Japanese phase 3 study involving participants over 16 years-old with mild to severe AD (IGA 2-4, BSA 5-30%). Improvements in all assessments with delgocitinib 0.5% ointment bid were sustained throughout the study period with 51.9% achieving mEASI-50 at week 52 and 27.5% EASI-75 at week 52.

In both trials, therapy related AEs were predominantly mild. Besides, the most frequent AEs were nasopharyngitis (25.9%), contact dermatitis (4.5%), acne (4.3%), application site folliculitis (3.6%), influenza (3.4%), Kaposi's varicelliform eruption (3.4%), application site acne (3.2%) and herpes simplex (3.0%).

Delgocitinib is also presented as a cream formulation with two phase 3 (NCT04871711 and NCT04872101) leading to its EU approval in chronic hand eczema (CHE) in 2024. There was a phase 2b, double-blind, randomised, vehicle-controlled, trial that evaluated its efficacy and safety in adults with mild to severe AD (NCT03725722). At the end of the 8-week treatment period, IGA-AD 0/1 in the 20mg/ml (highest strength) was achieved by 48% of subjects, against 10.4% in the vehicle group. Likewise, 66% subjects in the highest formulation reached EASI-75, against 20.8% with vehicle. The cream was generally well tolerated with the most frequent AEs (>5%) being application site pruritus, upper respiratory tract infection, headache, atopic dermatitis and acne. Also, there were no serious AEs with the highest formulation.

All the trials provide a satisfactory data related to efficacy across short and long-term periods, supporting its use in acute flares and in disease management. The substantial reductions in mEASI, particularly the high proportion of patients reaching mEASI-50 and mEASI-75, reflect the drug's anti-inflammatory effects. Nevertheless, the studies are limited in their geographic scope, since the ointment is focus solely on Japanese patients, which may raise questions about its generalizability to broader populations. Even though the cream formulation has demonstrated signs of efficacy in AD after the Phase 2 study, intriguingly there is no evidence of planned or ongoing Phase 3 trials.

While delgocitinib is a promising topical treatment for both AD and CHE, some safety aspects still require further investigation. The fact that serious viral infections, such as Kaposi's varicelliform eruption, were relatively rare but still present, highlights a potential gap in safety data, especially in the real world. Additional studies focusing on broader and more diverse patient populations, real-world data from registries and longer treatment durations could provide more comprehensive safety data.

Brepocitinib

Brepocitinib, a JAK1/TYK2 dual inhibitor, completed phase 2b trials in mild-to-moderate AD patients (NCT03903822). Once-daily dosing of 1% showed EASI reductions of 70.1%, while twice-daily dosing achieved 75%, compared to 44.4% for vehicle [20]. IGA 0/1 rates ranged between 29.7% and 44.4% for active arms vs. 10.8%-13.9% for vehicle [20].

Despite marked efficacy, no phase 3 trials for brepocitinib are underway. Its notable short-term improvements leave gaps regarding long-term safety, sustained remission and real-world performance. The reasons for halting development remain speculative, emphasizing the need for transparency in next steps.

Lepzacitinib

Lepzacitinib, a "soft" JAK1/3 inhibitor, focuses on local action with rapid systemic metabolism to minimize systemic side effects. A phase 2b trial showed a 69.7% EASI reduction vs. 58.7% for placebo ($p = 0.035$). Safety data revealed no systemic AEs typical of other JAK inhibitors [21].

Although lepcacitinib's mechanism is innovative, the high placebo response (58.7%) raises concerns about design sensitivity. Further trials should validate efficacy, address placebo variability and confirm real-world advantages.

Tofacitinib

Topical tofacitinib, a JAK1/3 inhibitor, was evaluated in a phase 2a trial (NCT02001181), where EASI reductions reached 81.7% compared to 29.9% for vehicle ($p < 0.001$). Safety profiles were similar across groups despite higher AE rates in the vehicle arm [22].

Tofacitinib's rapid efficacy is promising, but the trial's short duration and lack of longer-term safety data necessitate further research to support its role in AD management.

Ivarmacetinib

Ivarmacetinib, a selective JAK1 inhibitor, was studied in a phase 2 trial (NCT04717310). While all doses showed EASI improvement, only the 0.5% group achieved significance (-66.9% vs. -40.2% for vehicle; $p = 0.002$). This dose also demonstrated favorable IGA and pruritus outcomes with good tolerability [23].

The unexpected efficacy of lower doses raises questions about ivarmacetinib's therapeutic window. Longer-term trials are needed to confirm these findings and its role in AD treatment.

Ifidancitinib

Ifidancitinib (ATI-502), a JAK1/3 dual inhibitor, showed gradual improvements during a 4-week open-label study (NCT03585296) with EASI reductions of 18%, 35% and 40% by weeks 1, 2 and 4, respectively [24].

Compared to other JAK inhibitors, ifidancitinib appears slower in onset, possibly positioning it more as a maintenance therapy. Larger, randomized studies are required to clarify efficacy, safety and long-term applicability. Table 1 summarizes the findings for the JAK inhibitors.

Topical Agent	Mechanism	Efficacy	Safety	Study Limitations
Ruxolitinib	JAK1/JAK2 inhibitor	1.5% cream: IGA 0-1 at week 8 (53.8% and 51.3%), EASI-75 (62.1% and 61.8%). Long-term (52 weeks): IGA 0-1 in 70% of patients.	Most common AE: application site burning. No serious AEs.	Lack of comparative studies with other treatments.
Delgocitinib	Pan JAK inhibitor (JAK1, JAK2, JAK3, TYK2)	mEASI-50 at week 4 (51.9%) and 75 (26.4%). Long-term (24-52 weeks): sustained improvement in mEASI.	Most frequent AEs: nasopharyngitis, contact dermatitis, viral infections.	Trials mainly conducted in Japan, limiting geographic generalizability. No phase 3 trials for the cream formulation in AD.
Brepocitinib	Dual JAK1/TYK2 inhibitor	EASI reduction of 70.1% (1% cream). IGA 0/1 in 29.7-44.4% for 1% cream once daily.	No serious AEs reported.	Short trial duration (6 weeks), no ongoing phase 3 trials, long-term efficacy and safety data lacking.
Lepzacitinib	JAK1/JAK3 inhibitor	EASI reduction of 69.7% with 2% cream bid.	No major AEs associated with systemic JAK risks.	High placebo response (58.7%). Further trials required to confirm "soft" JAK mechanism.
Tofacitinib	JAK1/JAK3 inhibitor	EASI improvement of 81.7% at week 4.	Safety profile similar to placebo.	Short-term trial (4 weeks), no long-term safety data.
Ivarmacetinib	JAK1 inhibitor	EASI reduction (56.1%-66.9%) across doses ($p=0.002$ for 0.5%).	Well-tolerated, no serious AEs reported.	Short trial duration (8 weeks), unusual dose-response pattern observed (lower doses more effective).

Ifidancitinib	JAK1/JAK3 inhibitor	EASI improvement of 40% at week 4.	No serious AEs.	Small sample size, open-label design, slower efficacy compared to other JAK inhibitors. Long-term safety and efficacy data lacking.

Table 1: JAKs.

Phosphodiesterase-4 (PDE4) Inhibitors

PDE4 modulates cytokines in various cell lines by degrading cyclic Adenosine Monophosphate (cAMP) and its Inhibition leads to intracellular cAMP accumulation, regulating genes and proteins such as IL-4, IL-5, IL-10, IL-13 and prostaglandin E2 involved in AD pathogenesis [6].

Crisaborole

Crisaborole, FDA-approved in 2016, was the first topical PDE4 inhibitor for mild-to-moderate AD in patients aged 2 years and older. Two pivotal 28-day randomized, double-blind, vehicle-controlled trials (AD-301/NCT02118766, AD-302/NCT02118792) showed ISGA 0/1 rates of 32.8% vs. 25.4% ($p = 0.038$) and 31.4% vs. 18% ($p < 0.001$), respectively. While effective, its efficacy is lower compared to topical JAK inhibitors, though no direct comparisons exist.

Crisaborole demonstrated a favourable safety profile with mild-to-moderate TEAEs comparable to vehicle. The most common AE was application site pain, reported more frequently in real-world use (31.7%) than clinical trials (4.4%) [25]. This discrepancy highlights the need for ongoing post-marketing surveillance to ensure findings align with real-world experiences.

A phase 3 open-label, 48-week extension trial confirmed crisaborole's long-term safety with low TEAE frequencies [26]. This makes it suitable for maintenance therapy, particularly for patients prioritizing safety and tolerability. Despite being less potent, crisaborole's milder AE profile and robust long-term data make it ideal for children and those seeking safer continuous use, unlike JAK inhibitors, which may be better suited for acute flares or severe disease.

Roflumilast

Roflumilast, a potent PDE4 inhibitor, was recently approved for mild-to-moderate AD in patients aged 6 and older based on phase 3 randomized controlled trials involving over 1,200 participants. At Week 4, vIGA-AD success (clear or almost clear skin plus ≥2-grade improvement) was achieved by 31.3% of patients vs. 14.1% with vehicle ($p < 0.0001$). Significant improvements were also seen in EASI-75 (42.7% vs. 20.6%; $p < 0.0001$) and itch symptoms with reductions noted as early as 24 hours after application [27].

Both arms reported low TEAE rates with no serious AEs or discontinuations due to AEs. Tolerability was favourable; over 90% of participants reported no or mild sensations during the trial. Long-term data from open-label extension studies further supported roflumilast's sustained efficacy. After 56 weeks, 65.7% of participants achieved EASI-75, while flexible dosing regimens enhanced convenience and adherence. Common AEs were COVID-19, upper respiratory infections and headache with only 3% discontinuing due to AEs [28]. Roflumilast's strengths lie in its efficacy, tolerability and suitability for long-term, maintenance therapy. However, real-world data is limited and head-to-head comparisons with other PDE4 inhibitors or JAK inhibitors are needed. Such studies could clarify its relative efficacy, safety and patient satisfaction, contributing to improved decision-making.

Difamilast

Difamilast, approved in Japan in 2021 for patients aged 2 and older, selectively targets PDE4 subtype B. A phase 3 double-blinded study with 364 participants demonstrated significant efficacy with 38.46% achieving IGA 0/1 vs. 12.64% for vehicle ($p < 0.0001$). EASI-50, 75 and 90 outcomes also favoured difamilast [29]. Difamilast's safety profile was strong with fewer TEAEs in the active arm (17.6% vs. 28% for vehicle). Application site pain, often seen with PDE4 inhibitors, was not observed. This unique feature makes difamilast appealing for patients with sensitive skin or irritated lesions. Worsening AD was the most common TEAE, reported in 3.8% of the active arm vs. 12.1% for vehicle with treatment-related AEs being rare.

No serious AEs or severe abnormalities in clinical assessments were observed. Drug discontinuation rates due to AEs were lower in the difamilast group (3.8% vs. 11.5% for vehicle). While promising, long-term studies are needed to confirm its efficacy and safety in chronic use. Head-to-head trials comparing difamilast to other PDE4 inhibitors or JAK inhibitors are also necessary to better delineate its role in AD treatment. Table 2 summarizes the data for the PDE4s.

	Crisaborole	Roflumilast	Difamilast
Primary Endpoint Success	ISGA score 0/1: AD-301: 32.8% vs 25.4% (p=0.038); AD-302: 31.4% vs 18% (p<0.001)	vIGA-AD Success at Week 4: 31.3% vs 14.1% (p<0.0001)	IGA 0/1 with ≥2-grade improvement: 38.46% vs 12.64% (p<0.0001)
Other Efficacy Metrics	No direct comparison to other therapies,	EASI-75: 42.7% vs 20.6% (p<0.0001); Itch reduction observed as early as 24 hours	EASI 75 (42.86% vs 13.19%; *P* <.0001)
Application Site Pain	4.4% in trials; higher in real-world data (31.7%)	Minimal discomfort in >90% of participants	No reports of application site pain
Other TEAEs	Mild-to-moderate TEAEs, comparable to vehicle. Application site pain was most common	Low incidences of TEAEs; most common: COVID-19, URTI, nasopharyngitis, headache	TEAEs more common in the vehicle group; worsening AD and nasopharyngitis the most frequent
Long-term Safety	Low frequency of TEAEs over a 48-week extension trial	Long-term study shows sustained efficacy (EASI-75 in 65.7% at Week 56), low discontinuation rates (3%)	No long-term data available yet
Safety Profile	Adequate safety; well tolerated; no serious AEs. Application site reactions higher in real-world use	Safe with favourable tolerability; no major safety concerns	Good safety profile, lower TEAEs in active group than in vehicle; no serious AEs, mild worsening of AD most common
Discontinuation Due to AEs	Not highlighted	3.0% due to AEs	3.8% in active group vs 11.5% in vehicle group, primarily due to worsening AD

Table 2: PDE4s.

Transient Receptor Potential Vanilloid 1 Antagonists (TRPV1)

Transient Receptor Potential (TRP) channels are a superfamily of ion channels with diverse activation mechanisms, cation selectivity and biological functions. TRPV1, a key member, is a non-selective calcium-permeable cation channel activated by heat, low pH, capsaicin and inflammatory mediators. Expressed in keratinocytes, masT-cells and sensory nerves, TRPV1 plays a significant role in skin physiology and pathology, including pruritus, barrier dysfunction and inflammation. TRPV1 overexpression in AD lesions leads to the release of pro-inflammatory and pruritic mediators [16].

Asivatrep

Asivatrep, a selective TRPV1 antagonist, has demonstrated preclinical efficacy by reducing IgE, IL-4, IL-13 levels, inhibiting mast cell degranulation and improving epidermal barrier function [30]. In a phase 3 trial (CAPTAIN-AD, NCT02965118), 240 patients with mild to moderate AD (≥12 years old) were treated with asivatrep for 8 weeks. The active group achieved IGA 0/1 in 36.0% of patients versus 12.8% in the vehicle group ($p < 0.001$), along with significant reductions in EASI scores and improvements in pruritus and sleep disturbances. Although outcomes were modest compared to JAK or PDE4 inhibitors, asivatrep may be beneficial for those who are intolerant to other therapies.

Tolerability was strong with TEAEs occurring in 14.7% of the active group versus 6.3% in the vehicle group, including mild AEs such as nasopharyngitis, urticaria and burning sensation. No serious AEs or discontinuations were reported.

Asivatrep's unique mechanism targets sensory pathways involved in itch and pain, differentiating it from JAK and PDE4 inhibitors that focus on cytokine signaling or inflammatory cascades. However, long-term safety data and direct comparisons with other topical AD therapies are still lacking, limiting full evaluation of its role in chronic treatment.

Decolonizing Agents

AD patients often experience *S. aureus* colonization, contributing to dysbiosis and disease severity. This colonization impairs barrier function, increases allergen sensitization, exacerbates Th2-associated inflammation and promotes cytokine production [16]. Strategies addressing the microbiome by reducing *S. aureus* and promoting healthy bacteria are emerging.

Niclosamide

Niclosamide, traditionally an antiparasitic, has been repurposed for *S. aureus*-related microbial dysbiosis. A phase 2 trial (NCT03009734) in 36 adults with mild to severe AD showed significant efficacy in reducing *S. aureus* CFUs (94.4% vs. 38.9%, $p = 0.0016$) and improving microbiome diversity. Niclosamide was well tolerated with minimal local reactions and no safety concerns.

Due to the mechanism of action, it may complement existing therapies targeting inflammation or barrier dysfunction. While promising, larger trials are needed to validate efficacy and explore its role in preventing bacterial-driven flares or infections. Combining niclosamide with other treatments could offer a comprehensive approach to AD management.

Other Molecules

Zileuton

Zileuton, a topical 5-lipoxygenase inhibitor, reduces leukotriene-driven inflammation. In a phase 2 trial (57 patients, 8 weeks), 30% of the active group achieved IGA 0/1 versus 4% in the vehicle group ($p = 0.02$). While improvements in pruritus and EASI were modest, zileuton cream showed strong tolerability and no serious AEs [31]. The topical formulation minimizes systemic exposure, avoiding hepatic risks associated with the oral version. However, its limited impact on pruritus and disease severity suggests a need for larger trials to confirm efficacy. Combination therapies addressing multiple pathways, such as inflammation and itch, could enhance its clinical utility. Research into AD subtypes with pronounced leukotriene-mediated pathways may clarify its potential.

Atuzabrutinib

Atuzabrutinib, a topical BTK inhibitor targeting B-cell and mast-cell signalling, was studied in a phase 2a trial (39 adults, NCT04992546) over 6 weeks, focusing on safety. No serious AEs were reported, though 47 TEAEs occurred during the double-blind period, indicating moderate AE risks. However, efficacy data on pruritus, EASI scores and quality of life are absent, limiting its clinical relevance. Future trials should prioritize efficacy endpoints alongside safety.

Emerging Molecules

ASN008 (sodium channel blocker), YR001 (ion channel inhibitor) and QLM3003 (mechanism unspecified) are in phase 2 trials, but no results have been published yet (NCT05870865, NCT06309355, NCT06058000). Further evidence is needed to clarify their roles in AD treatment.

Discussion

AD is a chronic inflammatory skin condition with significant impact on patients' quality of life, characterized by symptoms such as pruritus, erythema and skin barrier dysfunction. Historically, TCS and TCIs have been the cornerstone of AD treatment. However, their safety profiles and typically occurring AEs, such as skin atrophy, tachyphylaxis and systemic absorption, especially after long-term use limit their applicability. As an attempt to overcome that, novel topical agents have been emerging in recent years with a premise of more targeted treatment mechanisms with potentially better efficacy and safety profiles. This review aimed to evaluate the comparative effectiveness and safety of these newer agents, focusing on JAK inhibitors, PDE4 inhibitors, AHR modulators and other unique molecules, in adult patients with AD. The analysis showed that these novel topical agents generally demonstrate appropriate levels of efficacy when compared to traditional treatments in adults with mild to moderate AD.

JAK inhibitors have been emerging as a promising class of topical agents. The data show that they significantly reduce pruritus and eczema severity, often within a few days to weeks, suggesting that JAK inhibitors could present as an excellent alternative for patients unresponsive to traditional therapies or who have contraindications to it. Nonetheless, concerns regarding their safety profile warranted a black box warning from the FDA to these agents, which will require intense long-term safety evaluation.

Topical PDE4 inhibitors were shown to reduce AD severity. While the magnitude of improvement in EASI scores may not be as remarkable as with the ones seen with some JAK inhibitors, PDE4 inhibitors have the advantage of a favourable safety profile, making them suitable for long-term use. Still, crisaborole can cause local irritation, which may limit patient adherence. Newer PDE4s with improved efficacy rates and better tolerability could present as better options for the therapeutic arsenal.

AhR modulators has shown promising results in clinical trials, demonstrating efficacy comparable to mid-potency corticosteroids. AhR modulation represents a novel mechanism of action with the prospective to reduce both inflammation and oxidative stress. In our review, AhR modulators were found to improve both objective and subjective symptoms of AD with minimal safety concerns reported in short-term studies. Despite these promising results, these molecules are still relatively new and their long-term safety and efficacy remain to be fully elucidated. They may serve as valuable alternatives for patients who cannot tolerate traditional therapies or those seeking a steroid-sparing option.

Asivatrep, niclosamide, Zileuton and Atuzabrutinib represent promising emerging therapies with novel mechanisms of action. Asivatrep, a TRPV1 antagonist, targets sensory pathways involved in itch and inflammation, showing potential for symptom relief, particularly in pruritus. Niclosamide an anti-parasitic drug, has decolonization properties and can meliorate microbiome diversity. Zileuton, a 5-lipoxygenase inhibitor, reduces leukotriene production and inflammation, although its utility in AD is still being explored. Atuzabrutinib, a Bruton's Tyrosine Kinase (BTK) inhibitor, modulates B-cell and mast cell activation, offering a targeted approach to immune regulation in AD. These agents could broaden therapeutic options but require further clinical investigation to confirm efficacy, safety and long-term benefits.

One of the challenges moving forward is the necessity for comparative studies between these novel agents. Currently, most trials use vehicle/placebo as a comparator, rather than TCS, TCIs or other molecules. While such studies lead to their regulatory approval, real-world data comparing their efficacy, safety and cost-effectiveness against established treatments will be critical for guiding clinical decision-making. Furthermore, head-to-head trials may help clarify whether specific agents are more effective in certain phenotypes or severities of AD. For example, it is not yet clear whether biomarkers such as serum IL-4, IL13, IgE levels or the presence of filaggrin mutations can predict response to any of these newer treatments.

As new treatments continue to emerge, clinicians will have a growing number of options for treating AD. This presents both an opportunity and a challenge. At first, having multiple therapies allows for more individualized treatment approaches, potentially improving outcomes for patients with different AD phenotypes or those who have failed previous treatments. On the other hand, until more comparative data are available, clinicians may face difficulty in choosing between these new agents and the conventional TCS and TCIs. Moreover, cost may become a limiting factor, as newer therapies are often more expensive than traditional corticosteroids, for example. Asivatrep, niclosamide, Zileuton and Atuzabrutinib represent promising emerging therapies with novel mechanisms of action. Asivatrep, a TRPV1 antagonist, targets sensory pathways involved in itch and inflammation, showing potential for symptom relief, particularly in pruritus. Niclosamide an anti-parasitic drug, has decolonization properties and can meliorate microbiome diversity. Zileuton, a 5-lipoxygenase inhibitor reduces leukotriene production and inflammation, although its utility in AD is still being explored. Atuzabrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, modulates B-cell and mast cell activation, offering a targeted approach to immune regulation in AD. These agents could broaden therapeutic options but require further clinical investigation to confirm efficacy, safety and long-term benefits. One of the challenges moving forward is the necessity for comparative studies between these novel agents. Currently, most trials use vehicle/placebo as a comparator, rather than TCS, TCIs or other molecules. While such studies lead to their regulatory approval, real-world data comparing their efficacy, safety and cost-effectiveness against established treatments will be critical for guiding clinical decision-making. Furthermore, head-to-head trials may help clarify whether specific agents are more effective in certain phenotypes or severities of AD. For example, it is not yet clear whether biomarkers such as serum IL-4, IL13, IgE levels or the presence of filaggrin mutations can predict response to any of these newer treatments.

As new treatments continue to emerge, clinicians will have a growing number of options for treating AD. This presents both an opportunity and a challenge. At first, having multiple therapies allows for more individualized treatment approaches, potentially improving outcomes for patients with different AD phenotypes or those who have failed previous treatments. On the other hand, until more comparative data are available, clinicians may face difficulty in choosing between these new agents and the conventional TCS and TCIs. Moreover, cost may become a limiting factor, as newer therapies are often more expensive than traditional topicals, for example.

Conclusion

In conclusion, the emergence of novel topical agents represents a significant advancement in the AD landscape, providing more targeted alternatives to standard therapies. While the current data are promising, further research is needed to fully understand the long-term implications, cost-effectiveness and broader applicability of these molecules.

Conflicts of Interest

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Authors' Contributions

All authors have contributed equally to this work and have reviewed and approved the final manuscript for publication.

Ethical Statement

This project was exempt from IRB review as it did not qualify as human subject research under federal regulations.

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