International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	THERAPEUTIC PROGRESS IN SYSTEMIC TREATMENT OF MODERATE-TO-SEVERE ATOPIC DERMATITIS
DOI	https://doi.org/10.31435/ijitss.1(49).2026.4812
RECEIVED	14 January 2026
ACCEPTED	15 March 2026
PUBLISHED	27 March 2026
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THERAPEUTIC PROGRESS IN SYSTEMIC TREATMENT OF MODERATE-TO-SEVERE ATOPIC DERMATITIS

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ABSTRACT

Introduction: Atopic dermatitis (AD) is the most prevalent inflammatory skin disease characterized by severe pruritus, eczematous lesions, and impaired skin barrier function. Both pediatric and adult populations respond to it with considerable impairment in quality of life and psychosocial well-being. Until recently, treatment options were mostly non-specific, low in efficacy, and often with serious side effects, particularly in moderate to severe cases. Nonetheless, recent advances in understanding AD pathophysiology have led to development of biologics and small molecules that target molecular pathways in the immune system modifying disease processes. The first biologic approved for AD (dupilumab) emerged in 2017 and greatly improved disease outcomes paving the way for further novel therapies.
Aim of study: The objective of this review is to summarize current and evolving systemic therapies for moderate to severe atopic dermatitis, particularly biologics and Janus kinase inhibitors. We summarize key clinical trial data, compare efficacy and safety profiles of approved agents and suggest future avenues for directed therapeutic approaches.
Materials and Methods: The literature available in the PubMed database was reviewed using the following keywords: "Atopic dermatitis", "abrocitinib", "baricitinib", "monoclonal antibodies", "dupilumab", "Janus kinase inhibitor", "lebrikizumab", "nemolizumab", "tralokinumab", "upadacitinib".
Summary: The development of tailored therapeutic strategies for these patients poorly controlled by traditional therapeutics is a result of advancement in AD pathophysiology. These innovations have shown considerable efficacy in reducing disease burdens and improving quality of life, serving as a paradigm shift in the current clinical care landscape.

KEYWORDS

Atopic Dermatitis, Dupilumab, Monoclonal Antibodies, Janus Kinase Inhibitors

CITATION

Aleksandra Jaskulska, Dominika Błonka, Jan Pietrzak, Magda Skudzińska, Karolina Wołk, Janina Pohrybieniuk, Filip Kochański, Maria Irena Grys, Magdalena Bartold, Kamil Rajczyk. (2026) Therapeutic Progress in Systemic Treatment of Moderate-to-Severe Atopic Dermatitis. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4812

Introduction

Atopic dermatitis is a chronic relapsing inflammatory skin disease, with about 10-20% of children affected and up to 3-7% of adults in developed nations. As per a global account on AD 2022, in 2022 approximately 223 million individuals had atopic dermatitis and these involved around 43 million people aged 1-4 years. According to a U.S. study, 58% of patients with atopic dermatitis have mild disease, 35% have moderate, and 7% have severe forms, with moderate–severe disease being more prevalent in both adolescents and adults compared to younger children [1].

Pruritus is the main symptom of atopic dermatitis and is the main source of discomfort and the disease burden. Other cutaneous features include xerosis, erythema, vesiculation, excoriation, exudation, crusting, and in more chronic cases lichenification. The effect of atopic dermatitis, however, is felt well outside the skin. Persistent itching, visible lesions, sleep disturbances, and comorbid atopic conditions, including asthma or allergic rhinoconjunctivitis, can all severely impair daily functioning and lead to psychological distress, including anxiety, depression, and social withdrawal in many patients [28].

Typical topical therapies prescribed for atopic dermatitis (AD) are skin hydration with moisturizers and emollients, topical corticosteroids, topical calcineurin inhibitors, crisaborole and phototherapy [29]. Systemic therapy is generally initiated in more severe or treatment-resistant cases. Systemic agents commonly utilized are azathioprine, methotrexate, ciclosporin, mycophenolate mofetil. They are not officially approved for the treatment of atopic dermatitis by the EMA or FDA. Use is clinically based and has been recommended by the scientific communities. The low efficacy, possible toxicity of conventional treatment options, and high prevalence of uncontrolled disease underscore the criticality of safe, efficacious, and targeted approaches to AD disease which target the mechanism of pathophysiological pathology [5].

Successful application of biological and small molecule therapy for treatment efficacy in atopic dermatitis is based on validated clinical outcome methods which assess disease severity, degree and burden of

symptoms. The Eczema Area and Severity Index (EASI) is one of the most frequently implemented scales among clinical trials. Augmentation of AD lesion size and severity are done in four parts of the body. The final number of points to be reported is a composite of 0-72 points. The success of treatment is often estimated as a percentage improvement from baseline (e.g. EASI-50, EASI-75, EASI-90), and EASI-75 frequently serves as a main endpoint in crucial trials [31]. The Investigator's Global Assessment (IGA) is another standard tool, offering a static 5-point or 6-point scale to rate overall disease severity, with scores of 0 (clear) or 1 (almost clear) representing optimal outcomes [32]. Apart from objective signs, patient-reported measures like Peak Pruritus Numerical Rating Scale (NRS) and Dermatology Life Quality Index (DLQI) are commonly adopted to assess itch intensity as well as the psychosocial implications of the disease, respectively [33,34]. Together, these scales comprise an overarching assessment of therapeutic and patient-centered outcomes.

Pathophysiology of Atopic Dermatitis

In recent years, the understanding of AD pathogenesis can be said to have changed dramatically, highlighting the interplay of genetics, environmental exposures, cutaneous microbiome changes, and the type 2–based immune response [4].

An AD characteristic is the disruption of the epidermal barrier and its function opening the path for introduction of allergens, microbes, and irritants. This barrier dysfunction is associated with decreased expression of structural proteins like filaggrin (FLG), loricrin, and involucrin, and remodelling of stratum corneum lipids. While FLG mutations are known to be a significant risk factor regarding early-onset AD, emerging evidence suggests that patients with or without FLG mutations also may exhibit reduced filaggrin expression due to the engagement of inflammatory cytokines, especially IL-4 and IL-13 [2,3].

The immune response in AD is dominated by type 2 (Th2-driven), especially in acute lesions. These cytokines, including IL-4, IL-13, and IL-5, induce the production of IgE and eosinophil recruitment, but also downregulate barrier-related genes. In chronic lesions, other immune subsets are also playing roles in promoting disease progression, such as Th22 and Th17, in which Th22 cytokine IL-22 promotes epidermal thickening and keratinocyte dysfunction. Also, recent findings show that TSLP, IL-33, and OX40L are upstream mediators of type 2 inflammation in AD [3].

Perhaps the most challenging disease of AD is pruritus, now recognised to be the product of immune and neuronal pathways. IL-31 secreted by mobilized Th2 cells directly contributes through its association with IL-31RA in cutaneous sensory neurons, resulting in increased itch experience and persistent scratching. Neuroinflammation is additionally amplified by the rise in density of nerve fibres and upregulation of pruritogenic receptors in the skin [3].

Recent evidence has also drawn attention to epithelial-derived cytokines such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25, which signal initiation and upregulation of type 2-associated inflammation through dendritic cell and innate lymphoid cell activation. These cytokines are upstream regulators of Th2 polarization and have potential targets for new therapeutic approaches [4].

The cutaneous microbiota is another important aspect of AD pathogenesis. Staphylococcus aureus becomes extremely abundant in the lesioned skin and can make the disease worse by forming superantigens and biofilms that trigger immune cells, but also impairing skin barrier components. In addition, compromised microbial diversity, including beneficial commensals, like Staphylococcus epidermidis contributes to immune dysregulation and to flare susceptibility [2].

Finally, epigenetic factors and gene-environment interactions also become a more widely acknowledged player in regulating the onset and severity of AD. Early-life exposure to allergen, infections, the use of antibiotics, changing diet, obese status, cosmetics, strong detergents, pollution and microbial colonization all present environmental influences that interact with genetic variants in immune-regulatory genes to predict individual disease risk and therapy response [4,28].

Altogether, the pathophysiology of atopic dermatitis entails a multilayered disruption of the dermal immune system, where barrier dysfunction, type 2-driven inflammation, pruritus, microbial dysbiosis, and host genetics mutually reinforce each other. An understanding of these mechanisms has driven tailored therapies (biologics or small-molecule inhibitors) targeting particular inflammatory pathways to restore skin homeostasis.

Biological Therapies

Dupilumab

Dupilumab is a monoclonal IgG4 antibody that is 100% human, binds to the α-subunit of the IL-4 receptor, which is part of both the IL-4 and the IL-13 receptor complex thereby inhibiting the signal to both of them. These cytokines are critical to Th2 lymphocyte activation, pruritus, IgE production and skin barrier dysfunction [5].

The efficacy/safety of dupilumab have been reported in three important phase III clinical studies: SOLO 1, SOLO 2, and CHRONOS. In the SOLO trials, patients who received dupilumab weekly or every 2 weeks for 16 weeks experienced improved disease severity with significant effect compared to placebo (n = 1379). A proportion of patients who had an Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear skin) was 37–38% in the dupilumab groups versus 10% in the placebo group. Over the years, 51–52% of patient reported a 75% reduction in the Eczema Area and Severity Index (EASI-75) [6].

The CHRONOS trial (n = 740) evaluated dupilumab and topical corticosteroids as a long-term therapy for 52 weeks. EASI-75 was achieved in 65–67% of patients at week 52, while 39% achieved an IGA score of 0 or 1 for the majority of patients [7].

One such study evaluated 435 patients with moderate-to-severe atopic dermatitis (baseline IGA≥3), to whom more than 70% achieved an IGA score≤2 at month 4 after dupilumab initiation, including 42.8% with clear or almost clear skin (IGA 0/1). In patients with moderate-to-severe pruritus (NRS ≥3, n = 112), mean itch scores had dropped sharply from 7.0 to 2.8, and 70.5% reported ≥3 point reduction. In the BSA cohort (n=387), mean affected body surface area was decreased from 39.3% to 16.3%. These benefits were stable across all ages, sexes, and previous therapy history, consistent with clinically relevant decreases in disease severity, itchiness, and skin involvement seen in clinical trials [8].

According both to SOLO 1,2 and CHRONOS data, dupilumab received U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval in 2017, making it the first marketed fully human IgG4 monoclonal antibody that has been approved in AD [5]. It was approved for treatment of children aged ≥6 months with uncontrolled atopic dermatitis based on a Phase III trial in 2022 and is accessible for children in Europe since March 2023 [30].

In all these trials most of them that suffer from clinical complications were conjunctivitis, of which most were mild-to-moderate. Topical treatment with anti-inflammatory eyedrops was often sufficient, without the need to discontinue treatment [5]. Additionally, there were injection-site reactions, and less frequently, hypersensitivity reactions. Despite these, dupilumab has a good safety profile, is usually well tolerated in terms of its safety, albeit long duration of use [6,7].

Tralokinumab

A humanized monoclonal antibody IgG4, tralokinumab binds with high affinity to interleukin-13 (IL-13) and selectively inhibits IL-13Rα1/IL-4Rα heterodimer receptor signalling complex formation. Tralokinumab is highly specific for anti-inflammatory properties, while dupilumab inhibits IL-4 and IL-13, thus, reducing inflammation, pruritus and skin barrier dysfunction [5].

Phase III clinical trials have shown both the efficacy and safety of tralokinumab, with ECZTRA 1, ECZTRA 2, and ECZTRA 3 being the most prominent examples. For ECZTRA 1 and ECZTRA 2 (n = 802 and n = 794) adults with moderate-to-severe AD received tralokinumab (300 mg every 2 weeks) or placebo (PC-2) for 16 weeks. Results showed that compared with placebo, substantially more patients in the group receiving tralokinumab had clear or nearly clear skin (IGA 0/1) and at least 75% improvement in EASI-75. Among patients receiving tralokinumab, 38.9% reached EASI-75 in ECZTRA 1 to 26.2% in placebo [10].

The study also evaluated outcomes for patients who responded well to 16 weeks of tralokinumab treatment and continued treatment as indicated, decreased the frequency to every four weeks, or transitioned to placebo. At week 52, without topical corticosteroids (TCS), 55% of patients who continued treatments every other week continued to maintain EASI-75, and around 50% of those receiving monthly dosing. It indicates that every four week treatment is effective for most patients having a stable disease control defined as clear or almost clear skin, absent or barely itch when the itch is absent or slightly itchy. Those patients who relapsed on a 4 week schedule regained their response after resuming the initial dosing [11]. The ECZTRA 3 trial looked at tralokinumab combined with topical corticosteroids for 32 weeks. Results supported both improved clinical response and durability of treatment, with 56% of patients achieving EASI-75 by week 16, and sustained responses until week 32 [12].

Interim results from the ECZTEND study indicate that at more than two years follow-up, the efficacy of tralokinumab persisted, with 82.5% of patients obtaining EASI-75, 59.8% EASI-90 and 48.1% on IGA 0/1 among the assessed patients (n = 291 out of 345) [13].

Treatments by tralokinumab were well tolerated throughout the included studies. Mild-to-moderate conjunctivitis and upper respiratory tract infections were the most common side effects. Because of tralokinumab's narrower immunological target than dupilumab the risk of adverse effects is lower, for example, ocular side effects appeared fewer times in studies compared to monotherapy with dupilumab [10,12].

Following these results, by 2021 EMA and FDA approved tralokinumab for treatment of moderate-to-severe AD for adults as a safe and effective long-term therapy.

Lebrikizumab

It is a fully human high affinity IgG4 monoclonal antibody that selectively binds to interleukin-13, neutralizing it. Like tralokinumab, lebrikizumab targets a key cytokine involved in the pathogenesis of atopic dermatitis, including skin barrier dysfunction and Th2-mediated inflammation mechanisms.

In pivotal phase III clinical trials (ADvocate 1 and ADvocate 2), lebrikizumab showed meaningful efficacy in the patients with moderate-to-severe atopic dermatitis. By week 16, 58–59% of lebrikizumab patients achieved EASI-75 [14], while just 16% in placebo groups.

The ADhere trial evaluated lebrikizumab in combination with topical corticosteroids (TCS) with moderate-to-severe atopic dermatitis. At week 16, 41.2% of subjects being received lebrikizumab plus TCS had achieved IGA 0/1 vs. 22.1% receiving placebo plus TCS. EASI-75 was achieved by 69.5% vs. 42.2%, respectively [15].

The 2024 study measured impact of lebrikizumab on quality of life (QoL) and mental health in ADvocate 1 and 2. Outcomes were assessed by the Dermatology Life Quality Index (DLQI) and the Patient-Reported Outcomes Measurement Information System (PROMIS) of anxiety and depression. Patients had considerable QoL impairment and have mean DLQI scores higher than 15 (max score 30) at baseline. Moreover, approximately half of participants reported at least mild anxiety as well as approximately 40% reported at least mild depression, with scores of ≥55 (normal <55, mild ≥55 to <60, moderate ≥60 to <70, and severe ≥70) on the PROMIS. In 16 weeks of treatment with lebrikizumab, mean DLQI scores had improved to ≤5, indicating that lebrikizumab showed a significant impact on QoL. PROMIS Anxiety scores decreased by 7.43 and 4.95 points in ADvocate1 and ADvocate2, respectively, as compared to decreases of 1.51 and 0.82 points with placebo. Similarly, PROMIS depression scores were 7.42 points and 4.28 points higher in the lebrikizumab groups than in the placebo groups, where the scores were 2.46 and 2.00 points [16]. The results of this study demonstrated that lebrikizumab led to significant clinical improvements in measures related to QoL and mental health.

The most frequently reported unwanted outcomes were conjunctivitis, atopic dermatitis exacerbation, skin infections, eosinophilia without any clinical symptoms, and herpes virus infections [14,15]. Significantly, lebrikizumab has lower prevalence rates of ocular complications compared with dupilumab [5].

EMA and FDA conducted a validation of lebrikizumab in November 2023 and September 2024, respectively, for the treatment of adults and adolescents aged 12 years and above with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

Nemolizumab

Nemolizumab: an empiric humanised monoclonal antibody which, unlike other biologics, has an inflammatory targeting nature, and preferentially blocks IL-31 receptor alpha, one of the critical cytokines associated with pruritus pathophysiology. By targeting the itch pathway directly, it offers a fast and lasting relief, often in just a few weeks therefore, making it a potential method for the treatment of pruritus-dominant atopic dermatitis.

In phase II-trialled studies, nemolizumab led to significant reduction in pruritus severity (up to 60-70% reduction peak pruritus NRS score) and increase in EASI scores, DLQI score, sleep and quality of life in patients with moderate to severe AD and lichenified lesions. Nasopharyngitis and upper respiratory tract infection were the most frequent side effects [17].

Phase 3 trials ARCADIA 1 and ARCADIA 2 examined nemolizumab with concomitant topical therapy. The end point for both ARCADIA 1 and 2 trials met their coprimary level. By week 16, more patients who received nemolizumab plus TCS/TCI were achieving IGA success and EASI-75 vs placebo (IGA success: 36–

38% vs 25–26%; EASI-75: 42–44% vs 29–30%). Nemolizumab also improved itch (as early as week 1) and sleep (by week 16). Safety was similar between treatment and placebo groups [18].

On December 13, 2024, and EMA on February 12, 2025, approval of nemolizumab was granted for moderate-to-severe atopic dermatitis in patients aged 12 years and older. It is the first authorized monoclonal antibody, which specifically targets IL-31 receptor alpha, to block the signaling of IL-31, a neuroimmune cytokine promoting itch and inflammation.

JAK-Inhibitors

The Janus kinase (JAK) family which is JAK1, JAK2, JAK3 and tyrosine kinase 2 TYK2 are all involved in cytokine receptor signaling. Upon the interaction of cytokines, these kinases stimulate signal transducers and activators of transcription (STATs) that dimerize and translocate to the nucleus to modify gene expression. The inhibition of JAK activity can knock-out multiple pro-inflammatory pathways at the same time, which provides a more general effect than attacking one cytokine. Additionally, JAK inhibition could alleviate pruritus and improve skin-barrier function by stimulating the up-regulation of filaggrin expression, thus avoiding pruritus [19]. JAK inhibitors are considered well tolerated, but caution in using these agents together with other immunosuppressants and strong CYP3A4 inhibitors (clarithromycin and ketoconazole) and CYP2C19 metabolizers or strong inhibitors should be emphasised [5]. Also baseline screening is standard and periodic follow-up is advised for all JAK inhibitors. The first assessments should include CBC, renal and liver tests, lipids, creatine phosphokinase (CPK), as well as screen for hepatitis and tuberculosis, including chest radiograph. Safety monitoring throughout disease treatment is of paramount importance. CBC, renal and liver function tests, lipid profile, and CPK are needed. It is recommended to be done 4 weeks after starting therapy then at least 3 times a year for further treatment [5].

Abrocitinib

Abrocitinib is an oral JAK1 inhibitor approved for moderate-to-severe atopic dermatitis in patients aged ≥12 years. It modulates cytokine signaling via JAK1 mediated modes of signalling for JAK1-dependent pathways, showing high selectivity and rapid symptomatic relief.

In 2020 and 2021, there were major clinical trials of abrocitinib that established for which abrocitinib was approved by EMA and FDA. JADE MONO-1 and JADE MONO-2 showed that abrocitinib (100 mg and 200 mg) was dose-dependent in monotherapy. At week 12, 40–45% of patients on 100 mg and 63–70% on 200 mg were EASI-75 compared to 24–27% of patients in the placebo groups [20].

In the phase 3 JADE EXTEND trial, patients who completed 16 weeks in JADE MONO-1 or MONO-2 continued with up to 92 weeks of abrocitinib treatment. In an interim 48-week study, treatment-emergent adverse events were similar among 200 mg or 100 mg without topical medications (86.1% vs 80.7%), with the vast majority of these occurring at mild-to-moderate risk. Follow-up clinical response (IGA 0/1, EASI-75, PP-NRS4) increased during the extension period with a peak between weeks 24-36 followed by a plateauing.

Other JADE COMPARE comparison evaluated abrocitinib versus dupilumab and placebo. Dosage level of abrocitinib (100 mg) did not demonstrate a significant difference compared to dupilumab in these three key secondary endpoints. Its 200 mg effect is more effective than dupilumab with faster itch reduction (often within 6 days of starting treatment), though not EASI-75 in week 16. Although 200 mg and dupilumab were used, an IGA response was still not observed. The results suggest that abrocitinib 200 mg is more likely to elicit treatment benefit when compared with dupilumab for intense AE [21,22].

The most common side effects are nausea, headache, acne, herpes zoster, and lab abnormalities (e.g., thrombocytopenia, lipid profile changes) [23].

Baricitinib

Baricitinib, is orally administered, blocking specifically and reversibly JAK1 and JAK2, disrupting subsequent signals of several pro-inflammatory cytokines, like IL-4, IL-13 and IL-31, thereby attenuating the immune-mediated disease phenotypes of atopic dermatitis.

The drug was evaluated in BREEZE-AD1 and BREEZE-AD2 studies that were large phase 3, multicenter, double-blind, placebo-controlled trials to ascertain the efficacy and safety of baricitinib 2 mg and 4 mg daily for adults with moderate-to-severe AD. In patients with moderate to severe AD the primary endpoint vIGA-AD 0/1 was reached with baricitinib 4 mg and 2 mg with both BREEZE-AD1 (4 vs 2 vs 1 mg vs placebo: 16.8% vs 11.4% vs 11.8% vs 4.8%) and BREEZE-AD2 (13.8% vs 10.6% vs 8.8% vs 4.5%). The 4 mg baricitinib target met the secondary endpoint with patients reporting significant reduction in pruritus and

great improvement in sleep and QoL. The 2 mg dose showed good efficacy; however, the 1 mg dose was ineffective [19].

The BREEZE-AD3 study evaluated the safety and efficacy of baricitinib (2 mg and 4 mg daily) over time. The initial vIGA-AD 0/1 response was sustained at 68 weeks with both doses and no new safety concerns. Moreover, the BREEZE-AD4 and BREEZE-AD7 trials assessed baricitinib 4, 2, and 1 mg plus TCS versus placebo. Only 4 mg dose achieved the primary endpoint of EASI-75 at week 16 in both trials (BREEZE-AD4 4, 2, 1 mg, placebo: 31.5% vs. 27.6% vs. 22.6% vs. 17.2%, BREEZE-AD7 4, 2 mg, placebo: 31% vs. 24% vs. 15%, respectively). All doses achieved the secondary endpoint of itch reduction in BREEZE-AD4, compared to BREEZE-AD7, where key secondary endpoints EASI-75 and itch-NRS4 were only achieved by 4 mg dose [19].

The primary endpoint (EASI-75 wk16: 29.5% vs. placebo 8.2%) and most secondary endpoints including itch reduction and vIGA-AD 0/1 during the BREEZE-AD5 trial from the North American trial were addressed with a single baricitinib-based treatment, 2 mg (2 versus 1 mg versus placebo: 29.5% versus 12.9% versus 8.2%) [19].

Due to these trials, it was approved in Europe in October 2020 and received FDA approval in June 2021 for the treatment of moderate-to-severe atopic dermatitis and became one of the first oral JAK inhibitors to be prescribed for AD in this indication [19].

The most frequent adverse events reported by clinical trials after baricitinib use included an elevation of LDL cholesterol, headache, nasopharyngitis, upper respiratory tract and herpes zoster infections, diarrhea, and nausea [19,24].

Upadacitinib

Upadacitinib is an orally-administered JAK1-selective inhibitor that has a once-daily effect, and it may reduce immune activation in atopic dermatitis by blocking the downstream cascade of cytokine signaling on JAK1, such as IL-4, IL-13, IL-22, IL-31, and interferon-γ.

Indeed, the efficacy and safety of upadacitinib in AD have been reported in a number of phase III trials, including Measure Up 1 and Measure Up 2 that compared daily doses of 15 mg and 30 mg versus placebo in adolescents and adults with moderate-to-severe AD. At week 16, EASI-75 and vIGA-AD 0/1 response rates were significantly greater with upadacitinib versus placebo (EASI-75 in Measure Up 1: 79.9% for 30 mg, 69.6% for 15 mg, vs. 16.3% placebo; and vIGA-AD 0/1: 62.0%, 48.1%, vs. 8.4%) [25].

In AD Up trial, at week 16, upadacitinib with doses of 30 mg and 15 mg and topical corticosteroids performed also better on EASI-75 and vIGA-AD 0/1 assessments (77.1% and 64.6% vs. placebo 26.4%, and IGA 58.6% and 39.6% vs. placebo 10.9%) [25].

At week 16 in an upadacitinib-versus-dupilumab head-to-head trial, 71.0% of patients treated with upadacitinib vs. dupilumab (61.1% vs. 61.1%): EASI-75, EASI-100 were achieved at week 16 by 28%, vs. 8%, respectively [36]. Improvements in ease of application and quality-of-life had been found by week 1 and the same pattern was confirmed for upadacitinib in all second-level endpoints (faster itch relief after week 1, earlier than EASI-75 by week 2 and prolonged improvement of symptoms and quality of life, respectively) [26].

Serious infection, eczema herpeticum, herpes zoster, and laboratory-related adverse events were reported in a statistically significant greater proportion of upadacitinib whereas, the rates of conjunctivitis and injection-site reactions were higher in dupilumab patients [5].

Upadacitinib was approved by FDA, in 2022, and by the EMA in 2021 for patients (12 years and older) with refractory moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic therapies.

Discussion

Atopic dermatitis have seen widespread and diverse therapeutic avenues with the creation of targeted treatments, such as biologics and small molecule inhibitors. These therapies offer clinicians a variety of options with different mechanisms of action, efficiency profiles, and safety considerations. Clinicians are thus better qualified to individualize treatment strategies against the systematic basis of the disease to the individual patient to the extent such as age, past medical history, wish to get pregnant, severity of disease and predominant symptoms (e.g., pruritus, sleep disturbances).

Among biologics, dupilumab, an IL-4Rα antagonist, was approved for patients as young as six months, and is available because of its strong efficacy, long-term acceptable safety profile, and added benefit for type

2 comorbidities such as asthma or chronic rhinosinusitis with nasal polyps. Tralokinumab and lebrikizumab, both other IL-13 inhibitors, are also available in patients who cannot respond to or are intolerant of dupilumab. Indeed, these agents have improved significantly the severity of the disease, showing similarly favorable safety profiles. They are especially effective for those patients who prefer biologic therapy with less frequent dosing, although they may have more gradual onset and lesser short term efficacy than JAK inhibitors. As an IL-31 receptor A antagonist, nemolizumab targets the pruritic pathway in a novel manner and is shown to have significant early-onset effectiveness on itch, as soon as week 1, with long-lasting improvements in both sleep and quality of life, making it an attractive option in patients with predominant pruritus and sleep disturbances.

Concurrently, JAK inhibitors have become successful and effective oral therapies for moderate-to-severe atopic dermatitis, providing rapid attenuation of skin inflammation and pruritus. Both upadacitinib and abrocitinib are selective JAK1 inhibitors with strong efficacy and an early onset of action, making them useful for patients with an increased need for immediate symptom relief or for those who prefer oral over injectable treatments. Significantly, upadacitinib has been shown to be more efficacious than dupilumab in head-to-head trials with superior rates of complete skin clearance (EASI-100) and faster time to a clinical response. Abrocitinib has also demonstrated significant reductions in disease severity and quality of life in clinical studies, potentially a plus in those with an itch-relief focus. Baricitinib may be somewhat less potent, but is also one of the few choices that is considered useful, with particular benefit in patients who are refractory to systemic immunosuppressants, such as cyclosporine. Compared to biologics, which undergo subcutaneous injections every 2 to 4 weeks, JAK inhibitors can be absorbed orally (once daily) offering a convenient alternative. This method of administration may be more appealing to younger adults who prioritise ease of use and rapid relief of symptoms. Patients at this age are also associated with lower comorbidity and baseline risk for adverse events, making the benefit–risk profile of JAK inhibitors more favorable. Because of safety concerns associated with the use of JAK inhibitors (e.g. thromboembolic events, major cardiovascular events, infections, and laboratory abnormalities), appropriate patient selection has often been stressed. Routine baseline assessments, including complete blood count, liver enzymes, lipid profile, tuberculosis screening, viral hepatitis serologies, and periodic screening with follow-up studies, are ideal for safe administration.

The implementation and timing of clinical trials should remain conservative and standardised, given the age and preference of patients, the risk of a single adverse event and the coexistence of conditions such as asthma, cardiovascular diseases, and immunosuppression. Looking at both types of drug, JAK inhibitors exert their effects quickly, usually in two weeks, while biologics are slower: 4 weeks for lebrikizumab, 4–6 weeks for dupilumab, 4–8 weeks for tralokinumab. Of approved treatments, upadacitinib and abrocitinib demonstrate the greatest short-term effectiveness. Yet in long-term responders, biologics such as dupilumab, lebrikizumab, and tralokinumab confer continued clinical benefit and favourable safety profiles with long-term use. Dupilumab is now viewed as the safest modern systemic therapy in pregnant women or the individuals contemplating pregnancy, whereas JAK inhibitors should be avoided as risks and regulatory contraindications are apparent. Some care must also be taken since women's use in pregnancy data is still limited. In the end, the decision whether biologic or small molecule treatment should be made collectively with patients, their history and clinical picture, and the management of disease in the long-term.

Potential Routes for Treatment of Atopic Dermatitis

Researchers and clinicians aren’t simply looking for the next generation of approved therapies. Solutions that are currently available are opening the doors for potentially better outcomes. One of the most promising fields of innovation is the application of umbilical cord blood-derived mesenchymal stem cells. In preclinical and early-phase clinical trials, they have been shown to decrease production of inflammatory cytokines, re-establish skin barrier integrity and promote tissue repair in treatment models of inflammatory skin disease. Other novel strategies are the OX-40 inhibitors—OX-40 molecule, which is expressed on T cells in lesional AD skin as well as the novel monoclonal antibodies to induce IL-4Rα such as CBP201, CM310 or AK120 which inhibit IL-4 and IL-13 [9,27].

Conclusions

Atopic dermatitis management has undergone substantial change, from which patients in addition to clinicians can choose effective and targeted therapeutic options. Personalized treatments are feasible more than ever before. Ongoing researches, including head-to-head trials, and other, longer-term real world trials remain essential to further refine and optimize care improving sustained outcomes for patients.

Disclosure

Conceptualization: Aleksandra Jaskulska and Jan Pietrzak; Methodology: Janina Pohrybieniuk; Software: Filip Kochański; Check: Maria Grys and Karolina Wołk; Formal analysis: Kamil Rajczyk and Magdalena Bartold; Investigation: Maria Grys and Janina Pohrybieniuk; Resources: Filip Kochański; Data curation: Kamil Rajczyk; Writing - rough preparation: Aleksandra Jaskulska and Jan Pietrzak; Writing - review and editing: Magdalena Bartold and Dominika Błonka; Visualization: Magda Skudzińska; Supervision: Aleksandra Jaskulska; Project administration: Karolina Wołk and Dominika Błonka; Receiving funding - no specific funding. All authors have read and agreed with the published version of the manuscript.

Financing statement: This research received no external funding.

Conflict of interest: The authors deny any conflict of interest.

AI was utilized for two specific purposes in this research: Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgement in the analytical process.

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