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# TARGETED SYSTEMIC THERAPIES IN ATOPIC DERMATITIS A COMPARATIVE REVIEW OF BIOLOGICS AND JAK INHIBITORS

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## Abstract

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease characterized by eczematous lesions, intense pruritus, sleep disturbance, impaired quality of life, and substantial psychosocial burden. For patients with moderate-to-severe disease inadequately controlled by optimized topical therapy, targeted systemic therapies have transformed management. These therapies include biologic agents directed against type 2 inflammatory cytokine pathways and oral Janus kinase (JAK) inhibitors that suppress intracellular cytokine signaling. This narrative comparative review evaluates approved and guideline-supported targeted systemic therapies for

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AD, focusing on mechanism of action, efficacy, speed of response, safety, monitoring requirements, patient selection, and practical treatment decision-making. Biologics such as dupilumab, tralokinumab, lebrikizumab, and nemolizumab selectively target interleukin-mediated pathways and are generally positioned as durable long-term options with lower laboratory-monitoring burden. JAK inhibitors such as upadacitinib, abrocitinib, and baricitinib tend to offer rapid improvement in itch and skin signs but require careful risk stratification because of infection risk, laboratory abnormalities, and cardiovascular or thrombotic warnings. Evidence from pivotal trials, prescribing information, and contemporary guidelines supports individualized therapy selection based on disease severity, urgency of symptom control, comorbidities, age, route preference, monitoring feasibility, and patient values. Overall, biologics and JAK inhibitors should not be viewed as interchangeable agents but as complementary therapeutic classes.

## INTRODUCTION

Atopic dermatitis is a common chronic inflammatory dermatosis driven by skin-barrier impairment, immune dysregulation, neuroimmune itch pathways, and environmental triggers [11]. Moderate-to-severe AD is not merely a skin-limited disorder; it can cause persistent pruritus, sleep loss, psychological distress, impaired daily functioning, recurrent skin infections, and reduced quality of life [11,12].

Traditional systemic immunosuppressants such as cyclosporine, methotrexate, azathioprine, and mycophenolate have historically been used for severe disease, but their nonselective immunosuppressive profile and monitoring burden have encouraged development of targeted systemic therapies [2].

The current treatment landscape includes monoclonal antibody biologics and oral JAK inhibitors. Biologics interrupt defined extracellular cytokine pathways, especially IL-4, IL-13, and IL-31 signaling, while JAK inhibitors act intracellularly to reduce signaling from multiple cytokines involved in AD

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inflammation and itch [2,3,5,6]. The clinical challenge is no longer simply whether targeted systemic therapy works, but how to select the right class and agent for the right patient.

The uploaded comparative efficacy paper is useful as an evidence background because it summarizes clinical trial evidence for multiple targeted systemic therapies, but the present manuscript is deliberately structured as a comparative narrative review rather than a meta-analysis [1]. It does not calculate pooled estimates or indirect treatment rankings; instead, it translates available evidence into a practical clinical comparison of biologics and JAK inhibitors.

## 2. Aim and Scope

The aim of this review is to compare biologic therapies and JAK inhibitors used for moderate-to-severe atopic dermatitis with respect to mechanism, efficacy, onset of response, safety, monitoring needs, and practical patient selection. The review emphasizes adult and adolescent systemic therapy, with pediatric applicability noted where relevant. The review focuses on targeted systemic therapies and does not provide detailed comparison of topical agents, phototherapy, or conventional immunosuppressants except where they inform the positioning of targeted therapy.

## 3. Methods: Narrative Comparative Approach

This is a targeted narrative comparative review. Evidence was drawn from pivotal randomized trials, clinical practice guidelines, regulatory prescribing information, and high-impact reviews relevant to targeted systemic therapy in AD [1-15]. The uploaded comparative efficacy paper was used as a reference source for trial-based comparative context, but this manuscript does not reproduce its network meta-analysis methods [1].

Therapies were grouped into two major classes: biologics and JAK inhibitors. Biologics included dupilumab, tralokinumab, lebrikizumab, and nemolizumab. JAK inhibitors included upadacitinib, abrocitinib, and baricitinib, noting that regulatory approval varies by country. Outcomes emphasized

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included EASI-75, EASI-90, IGA 0/1, pruritus response, durability, adverse-event profile, monitoring, and treatment-positioning considerations.

Figure 1 shows the simplified mechanistic rationale for comparing these therapies. It links barrier dysfunction and type 2 inflammation to biologic targets and shows how JAK-STAT signaling provides a broader intracellular target for oral small molecules.

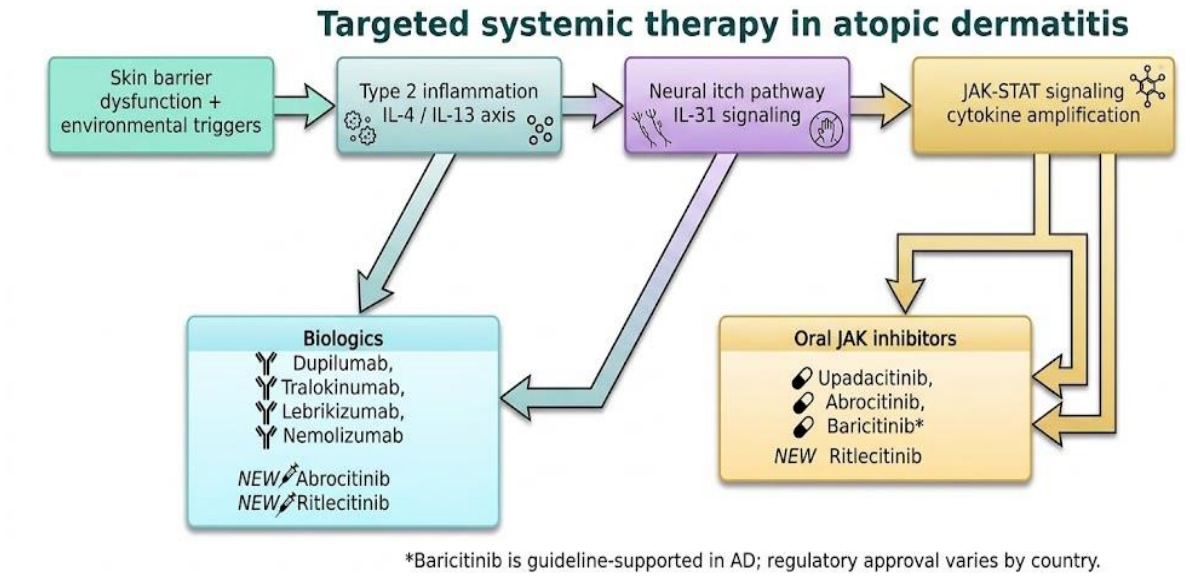


**Figure 1. Simplified mechanism map of targeted systemic therapies in atopic dermatitis. The figure shows how type 2 cytokine pathways support biologic targeting, while JAK-STAT signaling provides a broader intracellular target for oral JAK inhibitors**

### 4. Pathophysiologic Rationale for Targeted Therapy

Moderate-to-severe AD is dominated by barrier impairment and type 2 inflammation, particularly cytokine networks involving IL-4 and IL-13 [11]. These cytokines contribute to impaired barrier function, inflammation, epidermal thickening, pruritus, and susceptibility to infection. IL-31 is closely associated with itch signaling and neuroimmune activation, making it a relevant target in

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itch-dominant AD [6]. JAK-STAT signaling acts downstream of multiple cytokine receptors and therefore provides a broader intracellular target for oral small molecules [2,7,8].

This biology explains the major distinction between therapy classes. Biologics act selectively against individual cytokines or receptor components. JAK inhibitors interfere with downstream signaling across multiple cytokine pathways, which can produce rapid and broad clinical effects but also increases the need for safety screening and laboratory monitoring [2,7,8,14,15].

**5. Comparative Overview of Biologics**

Biologics are injectable monoclonal antibodies designed to block specific inflammatory pathways. They are generally well suited to patients who need sustained disease control, prefer or accept injection therapy, have contraindications to oral immunomodulators, or require a lower laboratory-monitoring burden. Their main limitations include delayed onset compared with JAK inhibitors, injection burden, access/cost barriers, and class-specific adverse effects such as conjunctivitis or keratitis in selected agents [2-6,10,13]. Table 1 compares major biologic options, their targets, practical strengths, cautions, and supporting citations

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**Table 1. Practical comparison of biologic systemic therapies for atopic dermatitis. The citation column identifies the pivotal trial, guideline, or regulatory source supporting the target, use, efficacy context, or safety note.**

| Therapy | Primary target | Route / dosing concept | Major strengths | Key cautions / limitations | Supporting citation(s) |
|---|---|---|---|---|---|
| Dupilumab | IL-4 receptor alpha; blocks IL-4 and IL-13 signaling | Subcutaneous; loading dose followed by every-2-week maintenance in adults | Most established biologic; broad age range; durable data; useful with atopic comorbidities | Conjunctivitis/keratitis, injection reactions, eosinophilic conditions in selected patients | [2,3,10] |
| Tralokinumab | IL-13 ligand | Subcutaneous; loading dose followed by every-2-week maintenance, with possible extension in responders | Selective IL-13 blockade; useful where biologic safety profile is preferred | Ocular events, injection reactions; response may be less rapid than JAK inhibitors | [2,4,13] |
| Lebrikizumab | IL-13 ligand | Subcutaneous induction followed by | Selective IL-13 biologic with strong | Ocular events, injection reactions; longer-term real-world | [5,14] |

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| Therapy | Primary target | Route / dosing concept | Major strengths | Key cautions / limitations | Supporting citation(s) |
|---|---|---|---|---|---|
| | | maintenance; interval may extend after response depending on label | week-16 responses in pivotal trials; maintenance flexibility | data still evolving | |
| Nemolizumab | IL-31 receptor alpha | Subcutaneous; used with topical corticosteroids and/or calcineurin inhibitors in AD | Targets itch-centered neuroimmune pathway; important option when pruritus is dominant | Approved with concomitant topical therapy for AD; not a pure monotherapy positioning in the label | [6,15] |

**6. Comparative Overview of JAK Inhibitors**

JAK inhibitors are oral small molecules that block intracellular cytokine signaling. Their main clinical advantage is rapid symptom relief, especially itch reduction, and high short-term skin-response rates in trials. This can be valuable for patients with severe itch, sleep disruption, extensive flares, or inadequate response to biologics. However, broader pathway inhibition requires careful risk assessment and monitoring [2,7-9,14,15]. Table 2 summarizes JAK inhibitor positioning, strengths, safety focus, and supporting citations

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**Table 2. Practical comparison of JAK inhibitors used or guideline-supported in atopic dermatitis. The citation column indicates the trial, guideline, or prescribing source supporting each comparison.**

| Therapy | JAK profile / positioning | Route / dosing concept | Major strengths | Monitoring and safety focus | Supporting citation(s) |
|---|---|---|---|---|---|
| Upadacitinib | JAK1-preferential inhibitor | Oral once daily; dose individualized by age, severity, and response | High efficacy and rapid itch/skin response; useful after inadequate systemic or biologic control | Boxed warnings; CBC, liver enzymes, lipids; serious infection, zoster, MACE, thrombosis, malignancy risk assessment | [2,7,14] |
| Abrocitinib | JAK1-selective inhibitor | Oral once daily; 100 mg with possible escalation in selected patients | Rapid itch relief; strong short-term efficacy; oral option for appropriate patients | Boxed warnings; CBC/platelets, lipids, hepatic/renal considerations; infection and thrombotic/CV risk assessment | [2,8,15] |
| Baricitinib | JAK1/JAK2 inhibitor | Oral once daily; | Guideline-supported | JAK class considerations; | [2,9] |

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| Therapy | JAK profile / positioning | Route / dosing concept | Major strengths | Monitoring and safety focus | Supporting citation(s) |
|---|---|---|---|---|---|
| | | regulatory approval for AD varies by country | systemic option in AD; oral therapy | laboratory monitoring; approval differs by jurisdiction | |

**7. Comparative Efficacy: What the Evidence Suggests**

Across pivotal trials and comparative evidence syntheses, JAK inhibitors generally show faster onset and higher short-term response rates than older biologics, particularly for itch improvement and EASI-75/EASI-90 outcomes [1,7,8]. In the published network meta-analysis used for background context, upadacitinib 30 mg, upadacitinib 15 mg, and abrocitinib 200 mg were among the most efficacious options at 12-16 weeks, while dupilumab and tralokinumab showed meaningful but generally lower short-term response estimates in that analysis [1]. Figure 2 displays contextual EASI-75 estimates from that published analysis; this review does not perform meta-analysis or pooling.

Newer biologics such as lebrikizumab and nemolizumab expand the biologic landscape. Lebrikizumab demonstrated clinically meaningful week-16 responses in phase 3 monotherapy trials, and nemolizumab demonstrated benefit in trials using background topical therapy, especially relevant to itch-centered disease [5,6]. Table 3 summarizes efficacy signals and cites the key evidence source for each comparison.

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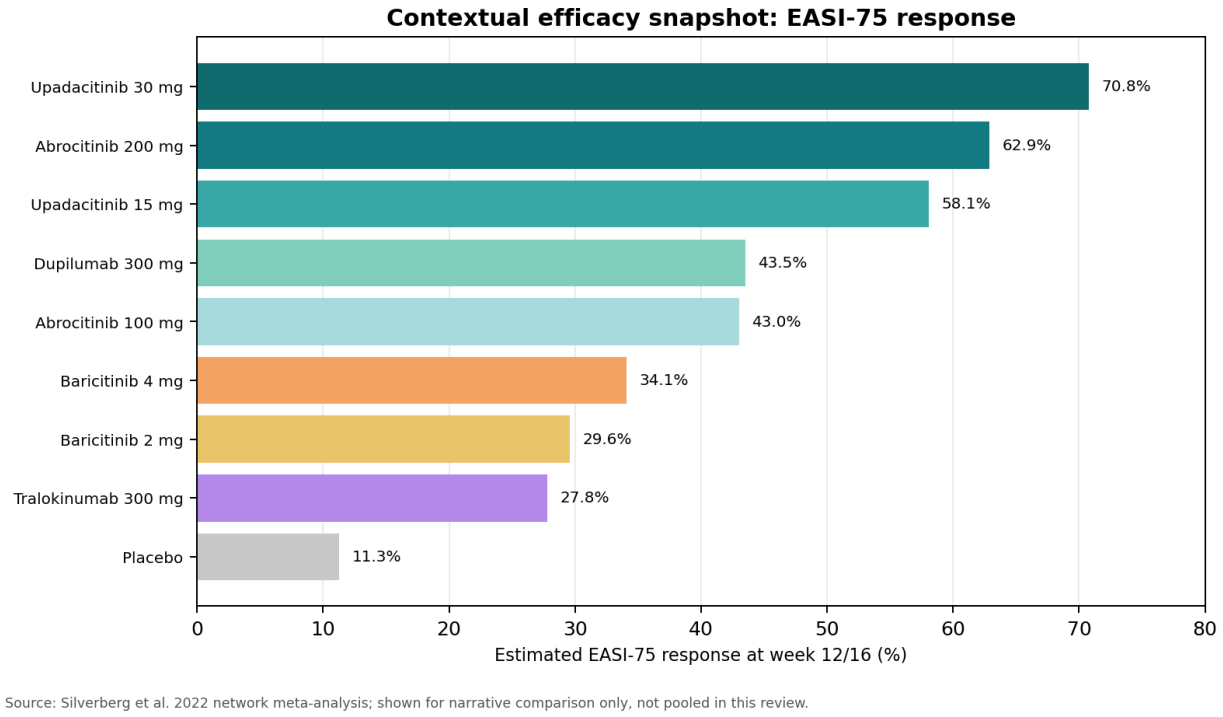


Figure 2. Contextual EASI-75 response estimates from a published network meta-analysis. These values are used only for narrative comparison and should not be interpreted as new pooled estimates from this review [1].

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Table 3. Evidence snapshot for narrative comparison. Values are contextual and not pooled by this manuscript; citations identify the trial or comparative synthesis supporting each row.

| Agent / dose | Class | Key trial or evidence context | Approximate week-12/16 skin response signal | Interpretation for review | Supporting citation(s) |
|---|---|---|---|---|---|
| Upadacitinib 30 mg | JAK inhibitor | Measure Up trials and comparative evidence syntheses | Highest EASI-75/EASI-90 and IGA response estimates in older NMA context | Very strong short-term efficacy; benefit-risk screening essential | [1,7,14] |
| Upadacitinib 15 mg | JAK inhibitor | Measure Up trials | High EASI-75 and IGA response; generally below 30 mg | Strong option when oral therapy appropriate | [1,7,14] |
| Abrocitinib 200 mg | JAK inhibitor | JADE MONO trials | High EASI-75 and itch response, near top tier in NMA context | Rapid itch-focused option; monitoring essential | [1,8,15] |
| Abrocitinib 100 mg | JAK inhibitor | JADE MONO trials | Moderate response; lower than 200 | May suit dose-sensitive patients but | [1,8,15] |

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| Agent / dose | Class | Key trial or evidence context | Approximate week-12/16 skin response signal | Interpretation for review | Supporting citation(s) |
|---|---|---|---|---|---|
| | | | mg | efficacy may be lower | |
| Dupilumab | Biologic | SOLO 1/2 and long-term data | Moderate-to-high durable response; broad real-world experience | Foundational biologic with strong long-term clinical familiarity | [1,3,10] |
| Tralokinumab | Biologic | ECZTRA 1/2 trials | Meaningful response with selective IL-13 blockade | Alternative biologic when IL-13 targeting preferred | [1,4,13] |
| Lebrikizumab | Biologic | ADvocate 1/2 trials | Week-16 IGA response approximately one-third to >40%; EASI-75 approximately mid-50% in pivotal evidence | Modern IL-13 option with flexible maintenance potential | [5,14] |

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| Agent / dose | Class | Key trial or evidence context | Approximate week-12/16 skin response signal | Interpretation for review | Supporting citation(s) |
|---|---|---|---|---|---|
| Nemolizumab | Biologic | ARCADIA 1/2 with topical background therapy | Week-16 EASI-75 around low-40% and IGA success mid-to-high 30% in ARCADIA context | Important itch-pathway biologic; best interpreted with background topical therapy | [6,15] |

**8. Speed of Response and Itch Control**

Rapid itch relief is one of the most patient-valued outcomes in moderate-to-severe AD because itch drives scratching, sleep fragmentation, mood disturbance, and skin damage [12]. JAK inhibitors often show early separation from placebo within the first weeks of therapy, making them attractive when rapid symptom control is clinically urgent [7,8]. Abrocitinib and upadacitinib are particularly notable for early pruritus improvement in clinical trials [7,8].

Biologics also reduce itch, but onset is often less immediate than with oral JAK inhibitors. Nemolizumab is mechanistically distinctive because it targets IL-31 receptor alpha, a pathway closely linked to pruritus. This makes it especially relevant for patients whose dominant burden is severe itch despite topical therapy; however, nemolizumab in AD is positioned with concomitant topical therapy, which should be acknowledged when comparing it with monotherapy data for other agents [6,15]

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**9. Safety, Monitoring, and Risk Stratification**

Safety differences are central to treatment selection. Biologics generally have favorable systemic safety profiles and usually do not require routine laboratory monitoring. Their most clinically relevant adverse effects include injection-site reactions, conjunctivitis, keratitis, hypersensitivity reactions, and rare eosinophilic complications depending on agent and patient profile [2,3,10,13,14].

JAK inhibitors require a more structured baseline and follow-up assessment. Before treatment, clinicians commonly consider infection screening, tuberculosis risk, hepatitis status where appropriate, vaccination status, complete blood count, liver enzymes, renal function, and lipid profile. During therapy, laboratory monitoring and adverse-event surveillance are required. JAK inhibitors carry warnings for serious infections, malignancy, major adverse cardiovascular events, thrombosis, and mortality; therefore, they are best used when expected benefit justifies these risks [2,14,15]. Table 4 contrasts class-level safety issues and provides citations for each comparison

**Table 4. Class-level practical safety comparison. The citation column identifies guideline or label sources supporting each class-level safety statement.**

| Domain | Biologics | JAK inhibitors | Supporting citation(s) |
|---|---|---|---|
| Route | Subcutaneous injection | Oral tablet | [2,10,13-15] |
| Onset | Moderate; often weeks | Often rapid; itch may improve early | [1,7,8,12] |
| Monitoring | Usually minimal routine laboratory monitoring | CBC, lipids, liver enzymes and risk-based infection screening | [2,14,15] |
| Common issues | Injection reactions, conjunctivitis/keratitis, | Acne, nausea, infections, zoster, | [2,10,13-15] |

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| Domain | Biologics | JAK inhibitors | Supporting citation(s) |
|---|---|---|---|
| | hypersensitivity | laboratory abnormalities, lipid changes | |
| Major risk focus | Ocular inflammation and hypersensitivity in selected patients | Serious infection, MACE, thrombosis, malignancy, mortality warnings | [2,14,15] |
| Best fit | Long-term control with lower monitoring burden | Need for rapid control when risk profile acceptable | [2,7,8] |
| Caution | Ocular disease, helminth infection, live vaccines depending on product label | Older age, cardiovascular disease, thrombosis risk, malignancy history, serious infection risk | [10,13-15] |

**10. Treatment Selection in Clinical Practice**

The most clinically useful comparison is not simply which drug has the highest response rate. A high response rate may be less important than safety in an older patient with cardiovascular disease, while rapid itch suppression may be the priority in a younger patient with disabling sleep loss and low risk factors. Shared decision-making is therefore central [2]. Figure 3 summarizes a practical decision frame and Table 5 links patient scenarios to class selection with supporting citatio

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## Clinical decision frame for biologics versus JAK inhibitors

| Patient priority | Therapy direction | Rationale |
|---|---|---|
| Need fastest itch/skin relief | Consider JAK inhibitor if risk profile acceptable | High efficacy, oral route, rapid onset |
| Need long-term safety simplicity | Consider biologic first | Lower routine laboratory monitoring burden |
| Conjunctivitis/ocular history | Individualize biologic selection | Some IL-4/IL-13 agents may increase ocular events |
| Older age/CV risk/thrombosis risk | Prefer biologic over oral JAK when possible | JAK boxed warnings and monitoring considerations |
| Dominant pruritus | Consider itch-focused strategy | IL-31 pathway targeting may help itch-dominant disease |

Figure 3. Practical treatment-selection framework for biologics versus JAK inhibitors. The figure emphasizes matching therapy to patient priority, safety profile, monitoring feasibility, and route preference.

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**Table 5. Clinical selection matrix for targeted systemic therapies in AD. The citation column indicates sources supporting the scenario-based treatment rationale.**

| Patient scenario | Preferred class direction | Reasoning | Supporting citation(s) |
|---|---|---|---|
| Severe uncontrolled itch with sleep loss and need for rapid relief | JAK inhibitor may be considered first if safe | Rapid onset and high short-term efficacy | [7,8,12] |
| High cardiovascular or thrombotic risk | Biologic often preferred | Avoids boxed-warning concerns of oral JAK inhibitors | [2,14,15] |
| Poor access to lab monitoring | Biologic often preferred | Less laboratory follow-up required | [2,10,13] |
| Need for long-term maintenance with stable safety profile | Biologic often preferred | Durability and lower monitoring burden | [2-5,10,13,14] |
| Failure or partial response to dupilumab/tralokinumab | Switch biologic or consider JAK inhibitor | Choice depends on risk profile and treatment goal | [2,5,7,8] |
| Dominant pruritus despite visible skin improvement | Consider itch-focused approach including nemolizumab where appropriate | IL-31 blockade may address neuroimmune itch | [6,12,15] |
| Need oral non-injectable therapy | JAK inhibitor if risk acceptable | Patient preference and adherence may favor oral route | [2,7,8] |

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| Patient scenario | Preferred class direction | Reasoning | Supporting citation(s) |
|---|---|---|---|
| History of recurrent severe infection | Biologic preferred; avoid or delay JAK if possible | JAK inhibitors carry higher infection-screening burden | [2,14,15] |

### 11. Special Populations and Practical Considerations

Age matters because approvals and safety data differ across pediatric, adolescent, and adult populations. Dupilumab has a broad pediatric labeling context in AD, whereas several other systemic therapies are labeled for adolescents or adults depending on jurisdiction [10,13-15]. Pregnancy potential, contraception, lactation, infection history, immunization status, and comorbid asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyps, eosinophilic disease, or ocular disease should be assessed before choosing therapy [2,10,13-15].

Access and affordability are also major determinants of real-world treatment selection. Biologics and JAK inhibitors may require prior authorization, step therapy, patient assistance programs, or specialist documentation of disease severity and previous topical therapy failure. In low-resource settings, the ideal therapy may not be the most practical therapy; monitoring feasibility, drug availability, and patient adherence must be considered.

### 12. Discussion

The targeted systemic treatment era has changed the therapeutic goals of atopic dermatitis. Previously, many patients with moderate-to-severe AD cycled through topical corticosteroids, calcineurin inhibitors, phototherapy, and conventional immunosuppressants with incomplete control or safety concerns. Biologics and JAK inhibitors now make clearer skin, itch reduction, sleep improvement, and improved quality of life realistic treatment targets for many patients [2,3,7,8].

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Biologics and JAK inhibitors occupy different but overlapping roles. Biologics are attractive long-term disease-modifying options because they target specific cytokine pathways with comparatively limited systemic monitoring requirements. Dupilumab remains a benchmark biologic because of extensive clinical experience and broad label context; tralokinumab and lebrikizumab refine IL-13-specific targeting, while nemolizumab adds an itch-centered IL-31 pathway strategy [3-6,10,13-15].

JAK inhibitors offer the advantage of oral administration and rapid multi-domain efficacy but require stricter safety screening. Upadacitinib and abrocitinib show strong short-term responses in pivotal trials and comparative evidence syntheses, but treatment decisions must account for boxed-warning risks, laboratory monitoring, infection risk, cardiovascular risk, thrombotic risk, and malignancy history [1,2,7,8,14,15].

The uploaded comparative efficacy study is useful because it shows the relative efficacy signal of several targeted therapies using trial-based network methods [1]. Nevertheless, a review intended for clinical use should not rank therapies on efficacy alone. It must also compare safety, monitoring, patient comorbidities, route preference, long-term data, and regulatory context. A patient with severe nightly pruritus and no major risk factors may reasonably favor an oral JAK inhibitor; another patient with cardiovascular risk, previous thrombosis, or difficulty with laboratory monitoring may be better suited to a biologic [2,14,15].

An additional issue is that the treatment landscape continues to evolve. Lebrikizumab and nemolizumab have expanded biologic options, and clinical guidelines continue to update recommendations as new evidence emerges [5,6]. Future comparative reviews should include long-term safety, head-to-head trials, real-world persistence, effectiveness in diverse skin tones, cost-effectiveness, and treatment sequencing after biologic or JAK inhibitor failure.

## 13. Limitations

This manuscript is a narrative comparative review and does not perform a systematic review, meta-analysis, or network meta-analysis. Therefore, it cannot provide pooled treatment estimates, formal

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ranking probabilities, or quantitative certainty assessments. Cross-trial comparisons must be interpreted cautiously because studies differ in inclusion criteria, disease severity, background topical therapy, endpoint timing, rescue medication rules, imputation methods, and placebo response. Regulatory approvals differ by region, so country-specific labels should be checked before applying treatment recommendations. Safety summaries in this review are not substitutes for full prescribing information or specialist clinical judgment.

## 14. Conclusion

Targeted systemic therapies have transformed the management of moderate-to-severe atopic dermatitis. Biologics and JAK inhibitors are both effective, but they differ in mechanism, route, speed, safety, monitoring, and ideal patient profile. Biologics are generally best suited for long-term disease control where safety simplicity and lower monitoring burden are priorities. JAK inhibitors are particularly valuable for rapid symptom control and high short-term efficacy when the patient's infection, cardiovascular, malignancy, and thrombotic risk profile is acceptable. Modern AD management should use shared decision-making and treat-to-target principles rather than selecting therapy by efficacy ranking alone.

## Declarations

**Ethics approval and consent to participate:** Not applicable. This review is based on previously published literature and regulatory information and does not involve new human or animal subjects.

**Consent for publication:** Not applicable.

**Data availability:** No new dataset was generated. All evidence discussed is available in the cited literature and regulatory documents.

**Competing interests:** To be declared by the authors before submission.

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Hafiza Ummara Hussain conceptualized the review, organized the manuscript structure, conducted the literature review, and drafted the manuscript. Jaweria Tanvir contributed to literature interpretation, comparative table development, manuscript editing, and critical revision. Nida Zahoor contributed to evidence verification, citation review, preparation of the safety and monitoring sections, and manuscript revision. Hafsa Junaid contributed to clinical interpretation, critical appraisal of the literature, and final manuscript review. Shaheen Fatima contributed to study planning, scientific supervision, critical intellectual revision, validation of the reviewed evidence, and final approval of the manuscript. Asad Bilal served as the corresponding author and contributed to methodology development, manuscript coordination, overall supervision, language editing, correspondence with the journal, and final approval of the manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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