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BIOLOGIC AND TARGETED THERAPIES IN ATOPIC DERMATITIS: A BIOMARKER-INFORMED FRAMEWORK FOR PERSONALIZED TREATMENT SELECTION

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ABSTRACT

Background: Atopic dermatitis is a chronic inflammatory skin disease characterized by pruritus, eczematous lesions, and impaired quality of life. Advances in understanding type 2 immune dysregulation have led to the development of biologic and targeted systemic therapies; however, treatment response remains heterogeneous, highlighting the need for personalized therapeutic strategies.
Objective: To review current biologic and targeted systemic therapies for moderate-to-severe atopic dermatitis, examine the role of clinical and molecular biomarkers in predicting treatment response, and propose a biomarker-informed framework for personalized treatment selection.
Methods: A narrative review was conducted of literature published between January 2020 and July 2024 using major scientific databases. Included publications comprised randomized controlled trials, cohort studies, systematic reviews, and expert consensus documents addressing systemic therapies, biomarker associations, and stratified treatment approaches in atopic dermatitis.
Results: Biologic agents, including dupilumab, tralokinumab, lebrikizumab, and nemolizumab, are associated with substantial improvements in skin inflammation and pruritus and demonstrate favorable safety profiles across diverse patient populations. Janus kinase inhibitors provide rapid symptom control but require careful patient selection due to safety considerations. Biomarkers such as thymus and activation-regulated chemokine, eotaxin-3, periostin, eosinophil count, and interleukin-13 gene expression contribute to the characterization of disease endotypes and may support biologically informed treatment decisions.
Conclusions: Biologic and targeted systemic therapies have transformed the management of atopic dermatitis; however, optimal outcomes depend on individualized treatment selection. Biomarker-informed approaches offer a rational framework to reduce empirical treatment cycling and advance precision medicine in atopic dermatitis, although further validation in real-world clinical settings is required.

KEYWORDS

Atopic Dermatitis, Biologic Therapy, Janus Kinase Inhibitors, Biomarkers, Personalized Medicine, Treatment Algorithm

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1. Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease affecting up to 20% of children and approximately 10% of adults worldwide, making it one of the most prevalent immune-mediated disorders across age groups (Drucker et al., 2020). The disease is characterized by recurrent eczematous lesions, intense pruritus, sleep disturbance, and a substantial impairment in quality of life. Beyond cutaneous symptoms, AD is associated with significant psychological distress, reduced work productivity, and increased healthcare utilization, contributing to a considerable socioeconomic burden on patients, families, and healthcare systems.

From a pathophysiological perspective, AD is increasingly recognized as a heterogeneous disease driven by complex interactions between epidermal barrier dysfunction, immune dysregulation, and neuroimmune signaling. Type 2 inflammation plays a central role in disease pathogenesis, with cytokines such as interleukin (IL)-4, IL-13, and IL-31 contributing to epidermal barrier impairment, chronic inflammation, and pruritus. These insights have transformed the conceptual framework of AD from a primarily skin-limited condition to a systemic immune-mediated disease with overlapping mechanisms shared with other atopic disorders, including asthma and allergic rhinitis (Davis et al., 2024).

Historically, systemic management of moderate-to-severe AD relied on broad immunosuppressive agents such as cyclosporine, methotrexate, azathioprine, and systemic corticosteroids. While these therapies can provide short-term disease control, their lack of pathway specificity, cumulative toxicity, and safety limitations restrict long-term use. The unmet need for safer and more targeted treatments has driven the

development of biologic therapies and targeted small-molecule inhibitors designed to selectively modulate key immune pathways involved in AD pathogenesis.

Over the past decade, the introduction of biologic agents—including dupilumab, tralokinumab, lebrikizumab, and nemolizumab—alongside oral Janus kinase (JAK) inhibitors, has fundamentally reshaped the therapeutic landscape of AD. These agents have demonstrated substantial improvements in disease severity, pruritus, and patient-reported outcomes, with more favorable safety profiles compared with traditional systemic immunosuppressants (Davis et al., 2024). As a result, systemic therapy for AD has transitioned toward mechanism-based treatment strategies aligned with disease biology.

Despite these advances, therapeutic response remains highly variable among individuals. Clinical heterogeneity is evident in differences in disease severity, distribution, chronicity, and symptom burden, particularly pruritus. In parallel, immunologic heterogeneity has been increasingly described, with distinct endotypes such as Th2-high and IL-13–dominant disease patterns influencing treatment responsiveness. Patient-specific factors—including age, comorbid atopic conditions, pregnancy status, and safety considerations—further complicate therapeutic decision-making and limit the effectiveness of a "one-size-fits-all" approach.

In this context, biomarker research has emerged as a critical component of precision medicine in AD. Circulating and tissue biomarkers such as thymus and activation-regulated chemokine (TARC/CCL17), eosinophil count, periostin, and IL-13 gene expression have shown potential in reflecting disease activity, defining immunologic endotypes, and predicting response to targeted therapies (Bakker et al., 2023; Renert-Yuval et al., 2021). Although most biomarkers remain investigational and are not yet routinely implemented in clinical practice, accumulating evidence supports their future role in guiding personalized treatment selection.

As the number of available systemic therapies continues to expand, there is a growing need for structured, evidence-based approaches that integrate clinical phenotype, biomarker profile, and patient-specific factors to optimize treatment outcomes. However, validated and widely adopted clinical algorithms for personalized therapy selection in AD remain limited.

This review synthesizes current evidence on biologic and targeted systemic therapies for moderate-to-severe AD, critically examines the role of clinical and molecular biomarkers in disease stratification, and proposes a pragmatic, biomarker-informed treatment framework designed to support personalized therapeutic decision-making in everyday clinical practice.

2. Methods

This narrative review was conducted to summarize current evidence on biologic and targeted systemic therapies for moderate-to-severe atopic dermatitis (AD), with a particular focus on mechanisms of action, clinical efficacy, safety profiles, biomarker relevance, and personalized treatment strategies.

A comprehensive literature search was performed using PubMed, Scopus, Web of Science, and ScienceDirect to identify articles published between January 2020 and July 2024. Search terms were combined using Boolean operators and included: *"atopic dermatitis," "biologic therapy," "dupilumab," "tralokinumab," "lebrikizumab," "nemolizumab," "JAK inhibitors," "upadacitinib," "abrocitinib," "biomarkers,"* and *"personalized treatment."*

Eligible publications included randomized controlled trials, cohort studies, systematic reviews, meta-analyses, and expert consensus statements involving human subjects with moderate-to-severe AD and reporting on systemic therapy outcomes or biomarker associations. Exclusion criteria comprised non-human studies, case reports, conference abstracts, and publications focusing exclusively on topical therapies.

Data extracted from included studies addressed therapeutic mechanisms, efficacy outcomes (including Eczema Area and Severity Index [EASI], Investigator's Global Assessment [IGA], and pruritus scores), safety and tolerability profiles, biomarker correlations (including TARC, periostin, eosinophil count, and IL-13 expression), and implications for personalized treatment selection. Priority was given to phase II and phase III clinical trials, high-quality reviews, and international guideline or consensus documents.

Findings were synthesized narratively and organized into thematic domains: (1) biologic and targeted small-molecule therapies, (2) biomarkers relevant to AD endotypes, and (3) phenotype- and biomarker-based treatment stratification. This integrative approach informed the development of a practical personalized treatment algorithm applicable to real-world clinical practice.

3. Overview of Current Biologic and Targeted Therapies for Atopic Dermatitis

Biologic therapies and targeted small-molecule inhibitors have transformed the systemic management of moderate-to-severe atopic dermatitis (AD), offering more precise modulation of type 2 inflammation compared with traditional immunosuppressants such as cyclosporine or methotrexate. Advances in understanding the pathophysiology of AD—particularly the central roles of IL-4, IL-13, and IL-31—have enabled the development of pathway-specific agents with improved long-term safety and sustained efficacy (Davis et al., 2024). Current systemic therapies may be broadly categorized into biologic monoclonal **antibodies** and **Janus kinase (JAK) inhibitors**, each with distinct mechanisms, advantages, and limitations.

3.1. Biologic Therapies Targeting the IL-4/IL-13 Axis and IL-31 Pathway

Dupilumab (anti–IL-4Rα)

Dupilumab was the first biologic approved for AD and remains the most widely used globally. By blocking IL-4Rα, it inhibits signaling of both IL-4 and IL-13, thereby suppressing key drivers of Th2 inflammation, improving epidermal barrier function, and reducing pruritus. Long-term studies demonstrate sustained efficacy and a favorable safety profile, including in adolescents and patients with comorbid asthma or chronic rhinosinusitis with nasal polyps (Davis et al., 2024; Drucker et al., 2020).

Tralokinumab and Lebrikizumab (anti–IL-13 monoclonal antibodies)

Tralokinumab and lebrikizumab selectively neutralize IL-13, a cytokine strongly implicated in epidermal barrier dysregulation, chronic inflammation, and disease persistence. Clinical trials demonstrate significant improvements in EASI and IGA outcomes comparable to dupilumab (Davis et al., 2024). Importantly, IL-13–selective agents are associated with lower rates of conjunctivitis, making them suitable alternatives for patients who develop ocular symptoms during IL-4Rα blockade (Bakker et al., 2023; Libon et al., 2024).

Nemolizumab (anti–IL-31Rα)

Nemolizumab targets IL-31 receptor α, disrupting a key pruritogenic pathway that predominantly influences neuroimmune signaling rather than cutaneous inflammation. In a landmark randomized trial, nemolizumab significantly reduced itch intensity and improved sleep quality when added to topical therapy (Kabashima et al., 2020). A subsequent phase 2B study confirmed its rapid antipruritic effects in moderate-to-severe AD (Silverberg et al., 2020). Although its primary regulatory approval is for prurigo nodularis, nemolizumab presents a promising option for itch-dominant AD phenotypes**.**

3.2. Targeted Small-Molecule Therapies: JAK Inhibitors

JAK inhibitors provide an oral alternative with broad intracellular inhibition of multiple cytokines involved in AD pathogenesis. Because they block downstream JAK–STAT signaling, their therapeutic effects extend beyond type 2 pathways, contributing to **rapid symptom relief,** often within days.

Upadacitinib (selective JAK1 inhibitor)

Upadacitinib demonstrates superior short-term efficacy compared with dupilumab, achieving faster improvements across EASI, IGA, and pruritus scores in a head-to-head randomized trial (Blauvelt et al., 2021). Its rapid onset of action makes it particularly valuable for patients with severe symptomatic burden or rapidly progressing disease.

Abrocitinib (selective JAK1 inhibitor)

Abrocitinib has also demonstrated rapid itch reduction and significant efficacy in adults and adolescents with moderate-to-severe AD in phase 3 JADE MONO-1 trials (Simpson et al., 2020). The speed of clinical improvement positions abrocitinib as an alternative for patients requiring immediate symptom control.

Safety Considerations for JAK Inhibitors

Despite high efficacy, JAK inhibitors require caution due to risks of infections, laboratory abnormalities, dyslipidemia, and rare thromboembolic events (Davis et al., 2024). They are contraindicated during pregnancy and require routine monitoring, making them suitable mainly for individuals without significant cardiovascular or thrombotic risk factors.

3.3. Comparative Efficacy and Safety

Across clinical studies, biologics and JAK inhibitors significantly improve disease severity and quality of life.

Biologics:

- offer **durable disease control**,
- have **high long-term safety**,
- require **minimal monitoring**,
- are well-suited to children, pregnant individuals, and those with comorbid asthma.

JAK inhibitors:

- provide the **fastest symptom relief**,
- are effective in **biologic non-responders**,
- require **careful risk stratification and monitoring**.

Comparative reviews and network meta-analyses confirm these therapy-specific strengths and highlight the importance of patient-tailored treatment selection (Drucker et al., 2020; Davis et al., 2024).

3.4. Summary Table

A comparative overview of currently available systemic therapies for moderate-to-severe AD is presented in Table 1.

Table 1. Comparative characteristics of systemic therapies for moderate-to-severe atopic dermatitis.

Drug	Target / Pathway	Class	Onset of Clinical Response	Common Adverse Events	Regulatory approval for AD (EMA/FDA)
Dupilumab	IL-4Rα (IL-4 & IL-13)	Monoclonal antibody	2–4 weeks	Conjunctivitis, injection site reactions	✓ / ✓ (AD ≥6 months; other indications vary by age)
Tralokinumab	IL-13	Monoclonal antibody	2–4 weeks	Conjunctivitis, headache	✓ / ✓ (≥12 yrs)
Lebrikizumab	IL-13	Monoclonal antibody	2–4 weeks	Conjunctivitis, headache	✓ / ✓ (≥12 yrs)
Nemolizumab	IL-31Rα	Monoclonal antibody	~2 weeks (pruritus relief)	Injection site reactions, headache	✓ / ✓ (AD ≥12 yrs; PN adults)
Upadacitinib	JAK1	JAK inhibitor	~1 week	Acne, URTIs, elevated CPK	✓ / ✓ (≥12 yrs)
Abrocitinib	JAK1	JAK inhibitor	~1 week	Nausea, headache, URTIs	✓ / ✓ (≥12 yrs)
Baricitinib	JAK1/JAK2	JAK inhibitor	1–2 weeks	Thrombosis, URTIs	✓ / not FDA-approved

Note. IL = interleukin; JAK = Janus kinase; URTIs = upper respiratory tract infections; CPK = creatine phosphokinase; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; PN = prurigo nodularis.

4. Biomarkers in Atopic Dermatitis: The Key to Personalization

The development of personalized treatment strategies in atopic dermatitis (AD) depends increasingly on the identification and validation of reliable biomarkers. These indicators—ranging from inflammatory chemokines to extracellular matrix proteins and gene-expression profiles—play essential roles in assessing disease severity, predicting therapeutic response, and monitoring pharmacodynamic changes during treatment. In the context of an expanding therapeutic landscape, biomarkers offer an opportunity to move beyond symptom-based treatment selection toward biologically informed decision-making.

Although many biomarkers remain investigational, growing evidence supports their utility in stratifying AD into biologically meaningful endotypes that correlate with differential treatment responses (Bakker et al., 2023; Libon et al., 2024; Renert-Yuval et al., 2021). Importantly, biomarker expression patterns often reflect underlying immune pathway dominance rather than visible clinical severity alone, highlighting their potential

value in identifying patients who may benefit most from specific targeted therapies. For clinical practicality, biomarkers relevant to AD can be organized into three functional categories: predictive biomarkers (treatment response), prognostic biomarkers (disease severity and chronicity), and pharmacodynamic biomarkers (on-treatment monitoring).

4.1. Key Biomarkers in Type 2 Inflammation

4.1.1. TARC (CCL17)

Thymus and activation-regulated chemokine (TARC/CCL17) is one of the most widely validated biomarkers in AD. Produced primarily by dendritic cells and keratinocytes in response to type 2 cytokines, TARC correlates strongly with disease severity, immune activation, and extent of skin involvement (Bakker et al., 2023). Multiple studies have demonstrated robust correlations between serum TARC levels and established clinical severity scores such as the Eczema Area and Severity Index (EASI).

TARC levels decrease rapidly following effective IL-4/IL-13 pathway blockade with dupilumab, making it both a marker of baseline disease activity and a sensitive pharmacodynamic indicator of therapeutic response. Elevated TARC concentrations are strongly associated with Th2-high endotypes, which typically demonstrate favorable and sustained responses to IL-4Rα or IL-13–targeted biologics (Renert-Yuval et al., 2021). Although not yet routinely used in daily practice, TARC remains one of the most promising candidates for future biomarker-guided treatment algorithms.

4.1.2. Eotaxin-3 (CCL26)

Eotaxin-3 (CCL26) is an IL-13–inducible chemokine involved in eosinophil recruitment and tissue infiltration. Elevated serum levels of eotaxin-3 correlate with disease severity and chronicity and are particularly prominent in patients with longstanding or lichenified AD (Libon et al., 2024). Because its expression is tightly linked to IL-13 signaling, eotaxin-3 may serve as a biomarker of IL-13–dominant inflammation.

Emerging evidence suggests that higher baseline eotaxin-3 levels may predict enhanced responsiveness to IL-13–selective monoclonal antibodies such as tralokinumab and lebrikizumab. This observation supports the concept that selective cytokine inhibition may be optimally effective in biologically defined subgroups rather than across the entire AD population (Libon et al., 2024).

4.1.3. Periostin

Periostin is an extracellular matrix protein induced by IL-13 and involved in tissue remodeling, fibrosis, and chronic inflammation. Elevated periostin levels have been associated with persistent, treatment-resistant, and lichenified forms of AD, reflecting long-term immune activation and structural skin changes (Renert-Yuval et al., 2021).

Because periostin reflects chronic IL-13–driven pathology rather than acute inflammation, it may be particularly useful in identifying patients with disease patterns less responsive to short-term anti-inflammatory strategies. In this context, periostin may help guide selection toward IL-13–targeted biologics in patients with chronic or relapsing disease phenotypes.

4.2. Broadly Available Clinical Biomarkers

4.2.1. Total IgE

Total serum IgE is frequently elevated in AD, especially in pediatric populations and patients with severe disease. However, its clinical utility is limited by low specificity, as elevated IgE levels are common across a wide range of atopic and non-atopic conditions. Although historically used to phenotype AD, IgE does not reliably predict response to specific biologic therapies and should not be used as a standalone decision-making tool (Davis et al., 2024).

4.2.2. Peripheral eosinophil count

Peripheral eosinophilia is a readily available marker of systemic type 2 inflammation. Higher eosinophil counts correlate with AD severity and may predict favorable response to IL-4/IL-13 blockade (Drucker et al., 2020; Bakker et al., 2023). However, eosinophilia alone is not sufficient to differentiate specific AD endotypes.

4.3. Molecular and Gene Expression Biomarkers

4.3.1. IL-13 gene expression

IL-13 mRNA expression in lesional skin represents a sensitive and pathway-specific marker of Th2 activation. Reductions in IL-13 gene expression occur rapidly following initiation of IL-4Rα or IL-13–targeted therapies, supporting its role as a pharmacodynamic biomarker (Libon et al., 2024). Although assessment currently requires skin biopsy and transcriptomic analysis, future development of less invasive assays may enable broader clinical application.

4.3.2. Emerging multi-omic biomarkers

Advances in proteomics, transcriptomics, and single-cell sequencing have suggested the existence of multi-omic signatures capable of distinguishing AD subtypes with greater precision (Renert-Yuval et al., 2021). These signatures may become foundational to precision medicine approaches and assist with selecting between biologics and JAK inhibitors.

4.4. Limitations and Future Perspectives

Despite promising progress, most biomarkers lack standardized cut-offs and are not yet integrated into routine clinical practice. Variability in assay methods, limited laboratory availability, and cost present ongoing barriers. Prospective validation in real-world cohorts and harmonization of biomarker thresholds will be essential to support widespread adoption (Bakker et al., 2023; Libon et al., 2024).

4.5. Summary Table

Key biomarkers relevant to phenotype classification and personalized therapy selection in AD are summarized in Table 2.

Table 2. Key biomarkers in atopic dermatitis: biological roles, clinical utility, and current availability.

Biomarker	Mechanism / Pathway	Clinical Role	Clinical Availability
TARC (CCL17)	Th2 chemokine attracting CCR4+ T cells	Predicts response to IL-4/IL-13–targeted biologics	Widely available (ELISA)
Eotaxin-3 (CCL26)	Eosinophil chemoattractant; Th2 inflammation marker	Correlates with severity; potential predictor of IL-13 response	Research only
Periostin	IL-13–induced matricellular protein	Marker of chronic inflammation and tissue remodeling	Research only
Total IgE	Non-specific Th2 activation marker	Elevated in severe AD; limited predictive value	Routine
Eosinophil count	Peripheral eosinophilia indicating systemic Th2 activation	Prognostic; may predict stronger biologic response	Routine CBC
IL-13 gene expression	Cytokine expression in lesional skin	Pharmacodynamic marker of biologic therapy response	Research (biopsy/transcriptomics)

Note. TARC = thymus and activation-regulated chemokine; IgE = immunoglobulin E; CBC = complete blood count; IL = interleukin.

5. Toward a Personalized Treatment Algorithm: Matching Drug to Patient

The expanding therapeutic landscape in atopic dermatitis (AD) presents both significant opportunity and increasing complexity. While biologic and targeted small-molecule therapies have demonstrated unprecedented efficacy, optimal treatment selection requires a shift from empirical prescribing toward a structured, individualized approach informed by disease biology, clinical presentation, and patient-specific factors (Davis et al., 2024; Renert-Yuval et al., 2021). In this context, personalized therapy aims to maximize therapeutic benefit while minimizing unnecessary treatment cycling and safety risks.

Precision-medicine strategies have been successfully implemented in fields such as asthma, psoriasis, and oncology; however, their application in AD remains at an earlier stage of development. Based on current clinical evidence, biomarker research, and expert consensus, therapy selection in AD can be conceptualized around three complementary pillars: (1) clinical phenotype, (2) biomarker-defined endotype, and (3) patient-

specific modifiers. Integrating these domains enables a rational, stratified decision-making framework applicable to routine dermatological practice.

5.1. Clinical Phenotypes and Therapeutic Implications

Phenotypic heterogeneity in AD reflects underlying immunologic diversity as well as differences in disease burden and symptom expression. Several clinical phenotypes consistently emerge in both clinical practice and the literature as relevant determinants of therapeutic response.

5.1.1. AD with airway or systemic type 2 comorbidities

Patients with concomitant asthma or chronic rhinosinusitis with nasal polyps (CRSwNP) frequently exhibit strong systemic type 2 immune signatures. Dupilumab, which inhibits IL-4 and IL-13 signaling, targets shared inflammatory pathways across skin and airway disease and has demonstrated cross-organ clinical benefit. Consequently, dupilumab is generally preferred in patients with multi-system allergic disease, where a single therapy may simultaneously improve cutaneous and airway manifestations (Bakker et al., 2023; Davis et al., 2024).

5.1.2. Itch-dominant AD phenotype

In a subset of patients, pruritus severity is disproportionately high relative to the extent of visible skin inflammation. This phenotype is increasingly recognized as being driven predominantly by IL-31–mediated neuroimmune signaling rather than cutaneous inflammation alone. Nemolizumab, an IL-31 receptor α inhibitor, has demonstrated rapid and clinically meaningful reductions in pruritus intensity and improvements in sleep quality in randomized trials, making it a rational option for itch-dominant AD (Kabashima et al., 2020; Silverberg et al., 2020). Where nemolizumab is unavailable, JAK1 inhibitors may also provide rapid itch relief through broader cytokine pathway suppression.

5.1.3. Rapidly progressive or highly symptomatic disease

Patients with severe disease activity, marked sleep disruption, or significant psychosocial burden may require rapid symptom control. JAK inhibitors, including upadacitinib and abrocitinib, consistently demonstrate the fastest onset of clinical improvement among currently available systemic therapies, often within the first week of treatment (Blauvelt et al., 2021; Simpson et al., 2020). Their broad intracellular mechanism allows simultaneous modulation of multiple inflammatory pathways, supporting their use in rapidly progressive or highly symptomatic AD.

5.1.4. Chronic lichenified or persistent AD

Patients with longstanding disease, chronic plaques, or marked lichenification may reflect a predominantly IL-13–driven inflammatory state. In these phenotypes, IL-13–selective monoclonal antibodies such as tralokinumab or lebrikizumab may be particularly effective by targeting cytokines implicated in epidermal barrier dysfunction and chronic tissue remodeling (Libon et al., 2024).

5.2. Biomarker Profiles and Endotype-Driven Treatment Selection

Molecular biomarkers provide additional insight into biologically distinct AD endotypes and may support therapy stratification when interpreted alongside clinical features.

5.2.1. Th2-high endotype

The Th2-high endotype is characterized by elevated levels of thymus and activation-regulated chemokine (TARC/CCL17), eosinophils, IgE, periostin, and increased IL-13 expression. These markers correlate with disease severity and reflect dominant type 2 immune activation. Patients exhibiting this profile generally demonstrate favorable responses to IL-4Rα blockade or IL-13–targeted biologic therapies (Bakker et al., 2023; Renert-Yuval et al., 2021).

5.2.2. IL-13–dominant signature

Elevated periostin and eotaxin-3 levels may indicate disproportionate IL-13 signaling within the broader Th2 spectrum. Emerging evidence suggests that such IL-13–dominant inflammatory patterns may be associated with enhanced responsiveness to IL-13–selective monoclonal antibodies, although direct predictive validation remains limited. This observation supports the concept that selective cytokine inhibition may be most effective in biologically defined subgroups rather than across the entire AD population (Libon et al., 2024; Renert-Yuval et al., 2021).

5.2.3. Th2-low endotype

Patients with low TARC levels, minimal eosinophilia, and limited IL-13 expression may exhibit reduced responsiveness to type 2–targeted biologics. These individuals likely represent a more heterogeneous immunologic

profile, potentially involving additional inflammatory or neuroimmune pathways. In such cases, JAK inhibitors, which provide broader cytokine modulation, may offer greater therapeutic benefit (Drucker et al., 2020).

5.2.4. Biomarkers as longitudinal tools

Beyond baseline stratification, biomarkers such as TARC and IL-13 gene expression decrease rapidly following effective therapy and may serve as pharmacodynamic indicators of treatment response. Although not yet incorporated into routine clinical practice, their future use could enable earlier assessment of therapeutic effectiveness and support dynamic treatment adjustments (Libon et al., 2024).

5.3. Patient-Specific Factors Affecting Treatment Selection

Personalized therapy selection must incorporate individual characteristics that influence safety, feasibility, and regulatory appropriateness.

5.3.1. Age considerations

Dupilumab is approved for the treatment of moderate-to-severe atopic dermatitis from 6 months of age, whereas abrocitinib and upadacitinib are approved from 12 years. Regulatory approval for IL-13–selective biologics in pediatric populations varies by region and indication. Overall, pediatric safety data strongly favor dupilumab due to its established long-term safety profile and minimal monitoring requirements.

5.3.2. Pregnancy and lactation

Based on available observational data and expert consensus, dupilumab is considered the most appropriate systemic therapy during pregnancy, whereas JAK inhibitors are contraindicated due to potential teratogenicity and systemic immunosuppressive effects (Deleuran et al., 2024).

5.3.3. Comorbidities and safety profile

Patients with increased risk of thromboembolic events, cardiovascular disease, or recurrent infections may not be suitable candidates for JAK inhibitors. Conversely, patients who develop conjunctivitis during dupilumab therapy may benefit from switching to IL-13–selective agents (Blauvelt et al., 2021; Davis et al., 2024).

5.3.4. Treatment burden and adherence

Biologics administered via infrequent injections may improve adherence in some patients, whereas oral JAK inhibitors may be preferred by individuals seeking non-injectable treatment options.

5.4. Integrated Treatment Algorithm

A practical, stepwise algorithm emerges when clinical phenotype, biomarker profile, and patient-specific factors are combined:

Step 1: Identify clinical phenotype

AD with asthma or CRSwNP → dupilumab
Itch-dominant AD → nemolizumab or JAK inhibitor
Rapidly progressive disease → JAK inhibitor
Chronic lichenified AD → IL-13–selective biologic

Step 2: Assess biomarkers

High TARC/eosinophils/IL-13 → IL-4Rα or IL-13 inhibitor
Th2-low profile → consider JAK inhibitor
Elevated periostin or eotaxin-3 → IL-13 inhibitor favored

Step 3: Apply patient-specific criteria

Pregnancy → dupilumab
Pediatric age → age-appropriate approvals
History of conjunctivitis → IL-13 inhibitor
Cardiovascular or thrombotic risk → avoid JAK inhibitors

Step 4: Evaluate response at 12–16 weeks

Adequate response → continue therapy
Partial response → intra-class switch
Non-response → consider JAK inhibitor escalation

Step 5: Long-term management

Laboratory monitoring for JAK inhibitors
Management of adverse effects
Reassessment of biomarkers where available

A comprehensive synthesis of this framework is presented in Table 3.

Table 3. Integrated personalized treatment framework for atopic dermatitis based on clinical phenotypes, biomarker signatures, and patient-specific factors.

Category	Clinical or Biomarker Feature	Preferred Therapy	Rationale / Interpretation
Clinical Phenotype	AD + asthma or CRSwNP	Dupilumab	Targets the IL-4/IL-13 axis shared across airway and skin inflammation, enabling benefit across skin and airway disease.
Clinical Phenotype	Itch-dominant AD	Nemolizumab (where available) or JAK inhibitor	IL-31 pathway blockade provides rapid itch improvement; JAK1 inhibitors also act quickly via broad cytokine suppression.
Clinical Phenotype	Rapidly progressive or severe symptomatic AD	Upadacitinib / Abrocitinib	Among the fastest onset of action among currently available systemic therapies; strong early reduction of pruritus and lesions.
Clinical Phenotype	Chronic lichenified AD (possible IL-13 dominance)	Tralokinumab / Lebrikizumab	IL-13 inhibitors may be more effective in chronic remodeling phenotypes.
Biomarker Profile	High TARC (CCL17), high eosinophils, elevated IgE	Dupilumab / IL-13 inhibitors	Indicates Th2-high endotype; strongest evidence for response to IL-4/IL-13 pathway blockade.
Biomarker Profile	High periostin or eotaxin-3	IL-13 inhibitors	Suggests IL-13–dominant inflammation and chronic skin remodeling.
Biomarker Profile	Low Th2 biomarkers (TARC, eosinophils, IL-13 expression)	JAK inhibitors	Th2-low endotype may respond poorly to biologics; JAK inhibitors target multiple pathways.
Biomarker Profile	High IL-13 mRNA expression	Dupilumab / Tralokinumab / Lebrikizumab	Reflects IL-13 pathway activation; strong predictor of targeted pathway response.
Patient-Specific Factors	Pregnancy or breastfeeding	Dupilumab	Best available safety data; JAK inhibitors contraindicated.
Patient-Specific Factors	Pediatric patient	Dupilumab (≥6 months for AD; age thresholds differ for other indications); JAK inhibitors (≥12 years)	Age-dependent approvals and safety considerations.
Patient-Specific Factors	History of conjunctivitis on dupilumab	Tralokinumab or JAK inhibitors	IL-13 inhibitors associated with lower conjunctivitis rates.
Patient-Specific Factors	Cardiovascular/thrombotic risk or recurrent infections	Avoid JAK inhibitors; prefer biologics	Safety concerns and boxed warnings for JAK inhibitors.
Patient-Specific Factors	Preference for oral vs injectable	JAK inhibitors (oral) or biologics (injectable)	Consider adherence, lifestyle, and convenience.
After 12–16 Weeks of Therapy	Adequate response	Continue current therapy	Maintain disease control.
After 12–16 Weeks of Therapy	Partial response	Intra-class switch (e.g., dupilumab → IL-13 inhibitor)	Optimize fit for endotype or phenotype and minimize under-treatment.
After 12–16 Weeks of Therapy	Non-response	Escalate to JAK inhibitor	Broader immunomodulatory effect for biologic non-responders.

Note. AD = atopic dermatitis; CRSwNP = chronic rhinosinusitis with nasal polyps; IL = interleukin; TARC = thymus and activation-regulated chemokine; mRNA = messenger ribonucleic acid; JAK = Janus kinase.

5.5. Expanded Case Scenarios

Case 1: Th2-High AD with Asthma

A 28-year-old patient with severe AD and poorly controlled asthma presents with elevated eosinophils and TARC.

Optimal therapy: Dupilumab

Rationale: Shared IL-4/IL-13–mediated inflammation across skin and airway disease.

Case 2: Itch-Dominant AD with Minimal Erythema

A 42-year-old patient reports severe pruritus (NRS 9/10) with limited visible inflammation and low eosinophil counts.

Optimal therapy: Nemolizumab

Rationale: Predominant IL-31–driven neuroimmune activation.

Case 3: AD During Pregnancy

A 31-year-old woman in her second trimester experiences worsening AD.

Optimal therapy: Dupilumab

Rationale: Most favorable pregnancy safety profile among systemic agents.

Case 4: Adolescent with Inadequate Response to Dupilumab

A 14-year-old patient shows partial improvement after 6 months of dupilumab therapy.

Optimal therapy: Upadacitinib

Rationale: Approved for adolescents ≥12 years and provides rapid, broad cytokine suppression.

6. Discussion

The rapid expansion of biologic and targeted systemic therapies has fundamentally reshaped the management of moderate-to-severe atopic dermatitis (AD), enabling a transition from non-specific immunosuppression toward mechanism-based and increasingly personalized treatment approaches. This review synthesizes current evidence on biologic agents, Janus kinase (JAK) inhibitors, and biomarker-driven stratification strategies, highlighting both the transformative potential of these therapies and the persistent challenges that limit full implementation of precision medicine in routine clinical practice (Davis et al., 2024; Drucker et al., 2020).

Biologic therapies targeting the IL-4/IL-13 axis, particularly dupilumab, have established a new standard of care for many patients with moderate-to-severe AD. Long-term clinical data demonstrate durable efficacy, sustained improvement in quality of life, and a favorable safety profile across diverse patient populations, including children and individuals with comorbid asthma or chronic rhinosinusitis with nasal polyps (Davis et al., 2024). The dual inhibition of IL-4 and IL-13 signaling addresses central drivers of type 2 inflammation, epidermal barrier dysfunction, and chronic disease persistence, explaining the broad and consistent clinical benefit observed in both randomized controlled trials and real-world studies.

The emergence of IL-13–selective monoclonal antibodies, such as tralokinumab and lebrikizumab, represents an important refinement within biologic therapy. By selectively targeting IL-13, these agents provide effective disease control while potentially reducing off-target effects associated with broader cytokine blockade. Clinical trial data suggest comparable efficacy to dupilumab in improving objective disease measures, with lower rates of conjunctivitis, which may be particularly relevant for patients who experience ocular adverse events during IL-4Rα inhibition (Bakker et al., 2023; Libon et al., 2024). These observations underscore the relevance of immunologic heterogeneity within AD and support the concept that not all patients require identical pathway inhibition to achieve optimal outcomes.

Nemolizumab introduces an additional dimension to AD management by targeting IL-31–mediated neuroimmune signaling rather than primarily cutaneous inflammation. Its pronounced antipruritic effects highlight the importance of recognizing itch as a partially independent disease driver, especially in patients whose symptom burden is dominated by severe pruritus and sleep disturbance (Kabashima et al., 2020; Silverberg et al., 2020). The success of nemolizumab reinforces the need to consider neurosensory pathways alongside inflammatory mechanisms when selecting systemic therapy, particularly in itch-dominant phenotypes that may not respond optimally to conventional anti–type 2 approaches.

In contrast to biologic therapies, JAK inhibitors such as upadacitinib and abrocitinib offer rapid and robust clinical improvement through broad intracellular inhibition of multiple cytokine pathways. Their ability to suppress signaling downstream of IL-4, IL-13, IL-22, and other mediators explains the rapid onset of action observed in clinical trials, often within the first week of treatment (Blauvelt et al., 2021; Simpson et al., 2020). This pharmacodynamic profile positions JAK inhibitors as valuable options for patients with rapidly progressive disease, severe pruritus, or inadequate response to biologic therapy. However, the broader immunomodulatory effects of JAK inhibition necessitate careful patient selection, regular laboratory monitoring, and individualized risk–benefit assessment, particularly in populations at increased risk for infections, thromboembolic events, or cardiovascular complications (Davis et al., 2024).

Biomarker research represents a central pillar in the evolution toward personalized medicine in AD. Biomarkers such as thymus and activation-regulated chemokine (TARC/CCL17), peripheral eosinophil count, periostin, and IL-13 gene expression provide mechanistic insight into disease activity and immunologic endotypes (Bakker et al., 2023; Renert-Yuval et al., 2021). Th2-high and IL-13–dominant profiles have consistently been associated with favorable responses to IL-4Rα or IL-13–targeted therapies, supporting the biological rationale for endotype-driven treatment selection. Nevertheless, several limitations hinder the routine clinical application of biomarkers, including variability in assay availability, lack of standardized thresholds, and incomplete correlation between single biomarkers and clinical outcomes (Libon et al., 2024).

An additional challenge lies in the dynamic nature of AD immunopathology. Biomarker profiles may evolve over time and in response to therapy, suggesting that static baseline measurements may be insufficient to fully capture treatment responsiveness. Pharmacodynamic biomarkers, such as early reductions in TARC or IL-13 gene expression following treatment initiation, offer promising tools for monitoring therapeutic response and identifying non-responders at an early stage (Renert-Yuval et al., 2021). However, these approaches remain largely confined to research settings, and prospective validation is required before widespread implementation in routine practice.

The personalized treatment algorithm proposed in this review integrates clinical phenotype, biomarker-defined endotype, and patient-specific modifiers, reflecting the multifactorial complexity of real-world therapeutic decision-making. By aligning disease biology with practical considerations such as age, pregnancy status, comorbidities, and treatment burden, this framework moves beyond single-parameter models and offers a more nuanced approach to systemic therapy selection. Case-based scenarios illustrate how this multidimensional strategy may be applied across diverse clinical presentations, including Th2-high disease with systemic comorbidities, itch-dominant phenotypes, and pediatric or pregnant patients.

Despite its conceptual strengths, the proposed algorithm requires validation through prospective clinical studies and real-world evidence to confirm its impact on long-term disease control, quality of life, and healthcare utilization. Furthermore, access to advanced systemic therapies remains uneven due to cost, reimbursement policies, and regional regulatory differences, potentially limiting the equitable adoption of personalized treatment strategies. Long-term safety data for newer agents, particularly JAK inhibitors, continue to evolve and will play a critical role in shaping future treatment paradigms.

In summary, biologic therapies and JAK inhibitors have revolutionized the management of moderate-to-severe atopic dermatitis, offering unprecedented opportunities for mechanism-based and individualized care. However, the realization of true precision medicine in AD will depend on continued refinement of biomarker-driven stratification, integration of clinical and molecular data, and validation of personalized treatment algorithms. As evidence continues to accumulate, individualized therapy selection has the potential to reduce therapeutic uncertainty, minimize unnecessary treatment cycling, and ultimately improve long-term outcomes and quality of life for patients with atopic dermatitis.

7. Conclusions

Biologic and targeted systemic therapies have fundamentally transformed the management of moderate-to-severe atopic dermatitis, offering safer, more effective, and mechanism-based alternatives to traditional systemic immunosuppressive treatments. As the therapeutic armamentarium continues to expand, clinical decision-making has become increasingly complex, underscoring the need for structured approaches that move beyond empirical treatment selection toward individualized, biology-driven strategies.

Current evidence supports the preferential use of IL-4/IL-13–targeted biologics in patients with Th2-high disease and concomitant airway involvement, IL-13–selective monoclonal antibodies in chronic or IL-13–dominant phenotypes, nemolizumab in itch-predominant atopic dermatitis, and Janus kinase inhibitors in rapidly progressive disease or in patients with inadequate response to biologic therapy. These distinctions

highlight the clinical relevance of immunologic heterogeneity in atopic dermatitis and emphasize that optimal therapeutic outcomes depend on aligning treatment mechanisms with dominant disease drivers and patient-specific characteristics.

Emerging biomarkers, including thymus and activation-regulated chemokine, eosinophil count, periostin, and interleukin-13 gene expression, provide valuable insight into disease endotypes and therapeutic responsiveness. Although their routine clinical implementation remains limited by issues related to standardization, accessibility, and cost, biomarker-informed strategies represent a critical step toward precision medicine in atopic dermatitis. In parallel, consideration of patient-specific factors such as age, pregnancy status, comorbidities, and treatment burden remains essential to ensure both efficacy and long-term safety.

The biomarker-informed treatment framework proposed in this review offers a pragmatic and clinically applicable approach to personalized therapy selection in atopic dermatitis. Future research should focus on prospective validation of biomarker-guided algorithms, harmonization of biomarker assays, and real-world evaluation of individualized treatment strategies. Continued integration of clinical, molecular, and patient-centered data has the potential to reduce therapeutic uncertainty, minimize unnecessary treatment cycling, and further improve long-term outcomes and quality of life for patients with moderate-to-severe atopic dermatitis.

Conflicts of Interest: The authors declare no conflicts of interest.

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