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Atopic Dermatitis Management: from Conventional Therapies to Biomarker-Driven Treatment Approaches

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Abstract

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder characterized by pruritus, skin barrier dysfunction, and immune dysregulation. It significantly impacts the quality of life and increases the risk of infections, sleep disturbances, and psychological distress. AD pathogenesis involves genetic predisposition, environmental triggers, microbiome alterations, and immune dysfunction. Traditional treatments such as topical corticosteroids, calcineurin inhibitors, and systemic immunosuppressants provide symptomatic relief but often fail to provide long-term disease control. The emergence of targeted biologics and Janus kinase inhibitors has transformed AD management by offering more precise and effective therapeutic options. However, treatment responses vary, highlighting the need for biomarker-driven personalized therapies. In this review, we explore the evolving therapeutic landscape of AD, emphasizing the emerging role of biomarker-guided treatment strategies. We highlight recent discoveries of therapeutic (OX40, IgE, IL-5, IL-31, IL-22, thymic stromal lymphopoietin) and diagnostic (TARC/CCL17, MDC/CCL2, filaggrin, sphingosine-1-phosphate, CXCL2) biomarkers that offer promising avenues for patient stratification and treatment monitoring. This review offers novel insight into how the convergence of biomarker research and therapeutic innovation can address current gaps in AD care. Future research should focus on refining biomarker-guided treatment strategies, optimizing therapeutic combinations, and addressing unmet patient needs. The integration of biomarker-guided strategies into routine clinical practice represents a critical step toward long-term disease control and improved quality of life for AD patients.

Key Words: Atopic dermatitis, Biomarkers, Targeted therapies, Precision medicine, Conventional treatment

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease characterized by intense pruritus, xerosis, and eczematous lesions. AD significantly affects and lowers the quality of life of millions of patients worldwide and poses a considerable healthcare burden (Lee, 2010; Weidinger *et al*., 2018). Triggered by irritants, allergens, and microbes, this disease typically manifests in infancy or early childhood and may persist into adulthood, with varying severity and chronic relapses (Margolis *et al*., 2014). Although AD is traditionally considered a pediatric disease, its increasing prevalence in adults highlights its lifelong impact and the need for comprehensive management strategies. The pathogenesis of AD is complex and involves a combination of skin barrier dysfunction, immune dysregulation, and genetic and environmental factors (Torres *et al*., 2019). Despite extensive research, the mechanisms underlying AD pathogenesis remain poorly understood.

An impaired epidermal barrier is considered a major predisposing factor for AD development. The skin barrier plays a crucial role in protecting against environmental insults, preventing excessive water loss, and limiting microbial colonization (Kim and Leung, 2018). Genetic mutations, particularly in the filaggrin (FLG) gene, and elevated serum immunoglobulin E (IgE) levels have been identified as strong risk factors for barrier dysfunction in AD (Clausen *et al*., 2015). Recent progress in molecular medicine has enabled genome-wide association studies and single-nucleotide polymorphism analyses, resulting in the identification of 62 genes associated with AD. Most of these genes encode skin barrier proteins and regulate both the innate and adaptive immune systems (Guttman-Yassky *et*

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al., 2017).

Immune dysregulation also plays a central role in AD pathogenesis. AD is a common skin disease mediated by T-helper 2 (Th2) cells via inflammasomes (Prakash *et al*., 2023). Mutations in the genes associated with Th2 cytokines and chemokines, including interleukin (IL)-4RA, IL-4, IL-13, IL-31, CCR5, and thymic stromal lymphopoietin (TSLP), have been identified in AD (Chien *et al*., 2007). The overproduction of these cytokines disrupts keratinocyte differentiation, impairs antimicrobial peptide production, and contributes to inflammation and itching (Jeskey *et al*., 2024). The innate immune system protects against pathogens and initiates the repair process following injury or trauma, thereby playing a crucial role in the inflammatory response (Prakash *et al*., 2023). Environmental triggers such as allergens, pollutants, climate, and irritants (e.g., soaps, detergents, and fragrances) further aggravate AD symptoms (Kim, 2015). In addition, psychological stress has also been implicated in AD, as it can activate neuroimmune pathways that worsen inflammation and pruritus (Lio and McCarthy, 2025).

The skin microbiome is another critical factor involved in the pathophysiology of AD. Healthy skin hosts a diverse range of commensal bacteria that contribute to immune regulation and skin barrier functions (Khadka *et al*., 2024). In patients with AD, the defense mechanisms of the skin against bacterial invasion are severely compromised, leading to decreased microbial diversity and overgrowth of pathogenic bacteria, particularly *Staphylococcus aureus* (Park *et al*., 2013). Studies have shown that over 90% of patients with AD have *S. aureus* colonization; these bacteria release toxins that trigger immune activation, increase inflammation, and disrupt the skin barrier (Altunbulakli *et al*., 2018; Conte *et al*., 2023). Whether microbiome alterations are a primary cause or a consequence of AD remains unclear; however, their role in disease exacerbation has been well documented.

According to the latest 2024 American Academy of Dermatology (AAD) guidelines (Davis *et al*., 2024), the treatment of AD in adults involves a stepwise approach beginning with topical therapies and progressing to systemic treatments for more severe cases. For patients with moderate-to-severe AD, biologics such as dupilumab (an IL-4/IL-13 inhibitor) and tralokinumab (an IL-13 inhibitor), along with Janus kinase (JAK) inhibitors such as upadacitinib and abrocitinib, have become standard therapeutic options. These biologics and JAK inhibitors have demonstrated efficacy in controlling AD by targeting key pathways involved in AD-related immune dysregulation (Davis *et al*., 2024). In addition to these therapies, recent studies have highlighted the potential role of herbal extracts (HEs) as novel agents in the management of allergic conditions, including AD. The pharmacological benefits of HEs demonstrated in both *in vitro* and *in vivo* AD models underscore their protective effects and therapeutic promise, particularly when used in practical extract forms; these findings support the potential inclusion of HEs in future AD treatment strategies (Lee *et al*., 2024).

Despite the increasing prevalence of AD worldwide, treatment options remain limited and many commonly used therapies lack a precise scientific and mechanistic basis. Although conventional treatments such as topical corticosteroids (TCS), moisturizers, topical calcineurin inhibitors (TCIs), phototherapy, and systemic therapies provide symptom relief (Calabrese *et al*., 2022), many patients experience recurrent flare-ups, inadequate response, or side effects from long-term use. No existing treatments offer sustained remission in individuals with moderate-to-severe AD, highlighting the significant unmet need for effective systemic treatments (Denby and Beck, 2012). The growing complexity and heterogeneity of AD necessitate a more individualized approach to therapy, emphasizing the importance of identifying and utilizing biomarkers that can guide personalized treatment strategies (Sims *et al*., 2021).

As insights into the pathogenic mechanisms of AD continue to expand, biological therapies have emerged as promising treatment options (Guttman-Yassky *et al*., 2013). Biological therapies mark a significant advancement in the treatment of allergic diseases such as AD by precisely targeting the key immune components involved in their pathogenesis. Unlike conventional treatments that generally suppress inflammation, biologics are specifically designed to modulate cytokines, immune cells, and signaling pathways that contribute to allergic inflammation, offering a more targeted and effective approach (Ramírez-Jiménez *et al*., 2023). Recent studies have identified novel biomarkers that may improve treatment selection, predict therapeutic responses, and facilitate early diagnosis. Identifying reliable biomarkers for emerging biological therapies, especially those targeting specific inflammatory pathways, is crucial for refining patient selection and improving treatment efficacy in AD (Alska *et al*., 2025).

This review aims to provide a comprehensive overview of the current and emerging treatment options for AD (Fig. 1, 2), focusing on novel biomarkers that may enhance diagnosis and guide personalized therapy. Understanding these advancements is essential to improve patient outcomes and bridge the gaps in AD treatment.

CONVENTIONAL THERAPIES FOR AD

Conventional treatments remain the foundation of AD management and serve as the first-line therapy for mild-to-moderate cases. Currently, the most commonly used topical treatments for AD, which mainly target local inflammation, include corticosteroids, calcineurin inhibitors, JAK inhibitors, and phosphodiesterase inhibitors (Weidinger *et al*., 2018). Conventional treatments for AD are classified as topical and systemic therapies (Table 1). Lately, various strategies have been developed to enhance AD management.

TOPICAL AGENTS

Topical treatments serve as the primary therapy for mild AD and are commonly used in patients with moderate-to-severe AD. Even in severe cases that require systemic therapy, topical agents are frequently used alongside systemic treatments to enhance disease management (Simpson *et al*., 2017).

Topical corticosteroids

The most widely used topical agents for the treatment of AD are TCS, many of which have already been developed and approved by the Food and Drug Administration (FDA). Corticosteroids have significant effects on the skin, including immunosuppressive, anti-proliferative, and anti-inflammatory actions. Systemic corticosteroids are very effective in reliev-

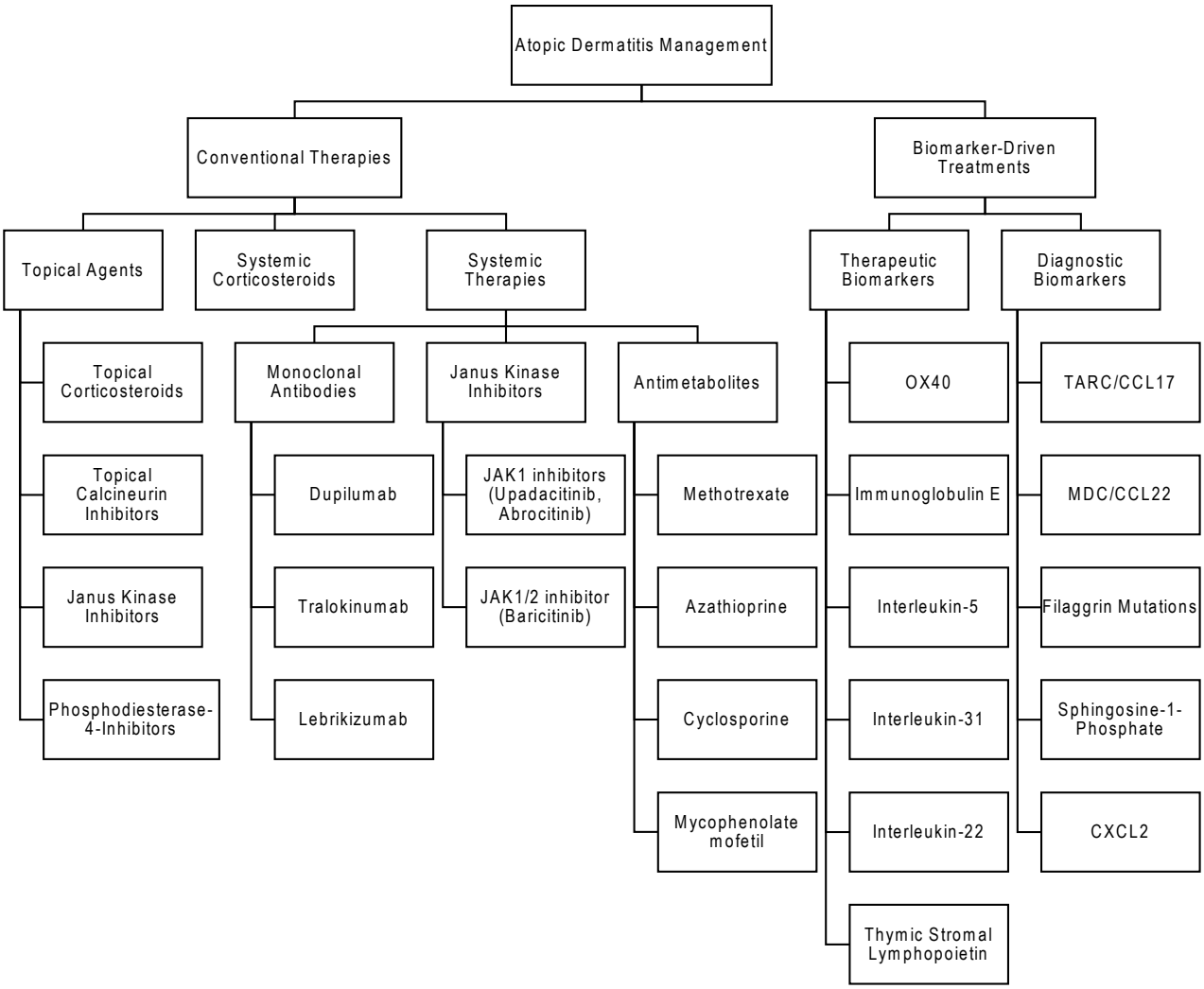

Fig. 1. A comprehensive overview of atopic dermatitis (AD) management, illustrating conventional therapies and biomarker-driven treatments. Conventional therapies include topical agents, systemic corticosteroids, and systemic treatments such as monoclonal antibodies, Janus kinase (JAK) inhibitors, and antimetabolites. Biomarker-driven treatments focus on therapeutic and diagnostic biomarkers, which play a crucial role in targeted therapy and personalized treatment approaches for AD.

ing acute attacks of AD; however, most guidelines and studies do not recommend long-term systemic steroid use in patients with AD. Therefore, they should only be chosen when other systemic options are not available and their use should be avoided, especially in children and adolescents with AD (Calzavara Pinton *et al*., 2018; Yu *et al*., 2018).

Indeed, TCS bind to glucocorticoid receptors, which initially exist in the cytoplasm. Upon binding to glucocorticoids, they translocate to the nucleus (Mehta *et al*., 2016). Then, the TCS-glucocorticoid receptor complex binds to glucocorticoid response elements in the promoter region of genes. This complex can activate or inhibit the transcription of mRNA and the synthesis of proteins, thereby regulating the transcription of other genes (Syed *et al*., 2020). In the context of AD, regulatory transcription factors such as nuclear factor-kappa B (NF-κB), activator protein 1, and nuclear factor of activated T cells (NFAT) play a role in suppressing inflammation by reducing the production of inflammatory cytokines and increasing the production of anti-inflammatory mediators.

In general, TCS are classified into seven categories according to intensity, from class 1 (highest intensity) to class 7 (lowest intensity), which must be selected considering the severity and area of use. Most studies recommend applying TCS twice daily, although some suggest that a once-daily application is sufficient for strong TCS. In most cases, TCS are discontinued once AD symptoms improve; however, in patients who relapse, maintenance therapy with once- or twice-weekly application is advised (Dölle *et al*., 2015). When discontinuing TCS, it is recommended to gradually reduce the frequency of application or transition to a lower potency compound to avoid flare-ups.

In patients with AD, TCS produces a rapid therapeutic effect, often leading to the disappearance of rashes within a few days. However, prolonged use may cause side effects, including reversible skin thinning, irreversible telangiectasia, and hirsutism (Hengge *et al*., 2006). Long-term use of a strong TCS

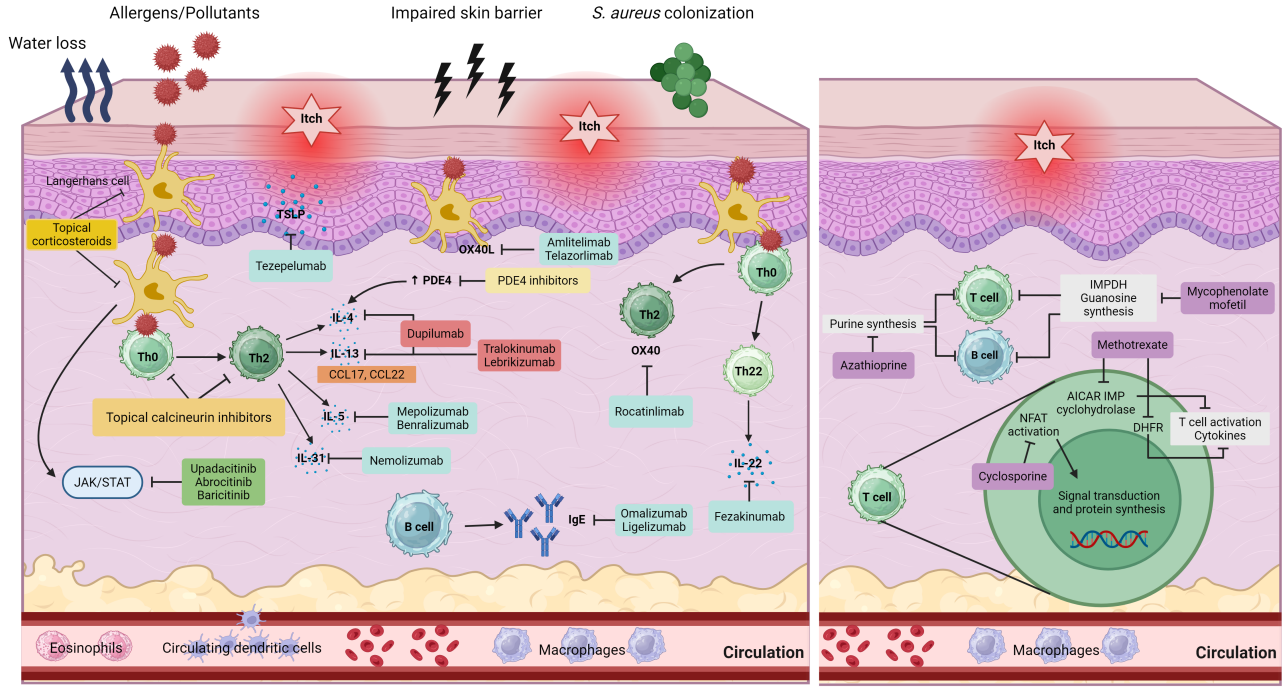

Fig. 2. Schematic representation of the pathophysiology of atopic dermatitis and the mechanisms of action of key conventional and biomarker-driven therapies. The disease is characterized by skin barrier disruption, allergen penetration, and microbial colonization, leading to Th2-dominant immune activation and cytokine overproduction. The left panel highlights targeted therapies which include monoclonal antibodies and biologics (e.g., dupilumab, tralokinumab, lebrikizumab, fezakinumab, omalizumab, ligelizumab, tezepelumab, amlitelimab, telazorlimab, rocatinlimab, nemolizumab, mepolizumab, benralizumab), small molecule inhibitors (e.g., JAK inhibitors, PDE4 inhibitors), and conventional treatments, such as topical corticosteroids and calcineurin inhibitors. The right panel depicts antimetabolites used in conventional systemic therapy, such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil, which broadly suppress T-cell activation and proliferation. Together, these therapies target distinct immune pathways, ranging from broad immunosuppression to biomarker-driven precision medicine in atopic dermatitis management. *S. aureus*, *Staphylococcus aureus*; Th, T helper cell; IL, interleukin; TSLP, thymic stromal lymphopoietin; PDE4, phosphodiesterase-4; IgE, immunoglobulin E; IMPDH, inosine monophosphate dehydrogenase; NFAT, nuclear factor of activated T-cells; AICAR IMP, 5-aminoimidazole-4-carboxamide ribonucleotide transformylase/inosine monophosphate; DHFR, dihydrofolate reductase.

around the eyes is not recommended, as it may increase the risk of developing cataracts or glaucoma in rare cases (Callen *et al*., 2007). Many patients experience side effects with TCS, possibly leading to reduced treatment adherence and suboptimal treatment outcomes. To address this, it is necessary to reduce steroid phobia by providing clear explanations to patients and caregivers to ensure appropriate selection and use of treatment (Charman *et al*., 2000).

Topical calcineurin inhibitors

For patients with AD who have difficulty tolerating TCS due to side effects, TCIs may be a safe and effective alternative treatment method that reduces the immune response by inhibiting T cell activation by decreasing the production of IL-2 (Gutfreund *et al*., 2013). The FDA-approved TCIs for the treatment of AD are 0.03% tacrolimus, 0.1% tacrolimus, and 1.0% pimecrolimus, which are used to treat moderate-to-severe AD (Ashcroft *et al*., 2005; Rubel *et al*., 2013). Tacrolimus 0.03% and pimecrolimus 1.0% can be used in children aged >2 years old. Although additional research is needed, they are safe enough for use in infants under 2 years of age (Patel *et al*., 2003). Tacrolimus 0.1% is approved for use only in patients with AD aged 16 years or older. Unlike TCS, one of the biggest advantages of TCIs is that they do not cause skin atrophy, even when used for a long period, and relieve the itching caused by AD (Kamata and Tada, 2023). Therefore, to prevent the recurrence of improved AD, regular application of TCIs 2-3 times a week is recommended as maintenance treatment (Paller *et al*., 2005; Breneman *et al*., 2008). Numerous clinical trials and meta-analyses have demonstrated that TCS and TCIs exhibit comparable efficacy in the treatment of AD (Broeders *et al*., 2016). However, TCIs are considered second-line treatments because of their high cost and potential side effects, such as itching and burning sensations. Although the FDA has issued a black box warning regarding the possible increased cancer risk associated with TCI use, long-term safety studies have shown a higher relative risk of lymphoma but not other cancers (Castellsague *et al*., 2018; Lam *et al*., 2021). Further long-term follow-up and research are necessary to precisely evaluate the potential cancer risks associated with TCI treatment.

JAK inhibitors

The JAK and signal transducer and activator of transcription (STAT) signaling pathway plays a crucial role in transmitting signals from key cytokines that interact with immune cells, keratinocytes, and peripheral sensory neurons, driving both inflammation and itching. This pathway is involved in the ac-

Table 1. Summary of topical and systemic therapies for atopic dermatitis

Category		Mechanism of Action	Indications	Common Adverse Effects	References
Topical Agents					
Topical corticosteroids (TCS)		Binds to glucocorticoid receptors, suppressing inflammation and immune response	Mild-to-moderate atopic dermatitis (AD)	Skin thinning, telangiectasia, hirsutism, rosacea, and acne	Calabrese *et al*., 2022
Topical calcineurin inhibitors (TCIs)		Inhibits calcineurin-dependent T cell activation, blocking pro-inflammatory cytokine production	Moderate-to-severe AD, steroid-resistant cases	Redness, localized burning, stinging, and itching	Calabrese *et al*., 2022
Janus kinase (JAK) inhibitors		Targets individual receptor-associated kinases, preventing the mediation of inflammatory signals	Moderate-to-severe AD unresponsive to topical therapies	Folliculitis, acne, nasopharyngitis, headache, nausea, and Kaposi's varicelliform eruption	He *et al*., 2024
Phosphodiesterase-4 (PDE-4) inhibitors		Blocks PDE-4 enzyme, increasing cAMP levels and reducing inflammation	Mild-to-moderate AD as a steroid alternative	Application site burning, pain, and rare systemic effects	Guttman-Yassky *et al*., 2019
Systemic Therapies					
Monoclonal Antibodies	Dupilumab	Blocks the IL-4 and IL-13 signaling pathways to modulate Th2 inflammation	Moderate-to-severe AD (first-line biologic therapy)	Injection site reactions, conjunctivitis, nasopharyngitis, and head and neck dermatitis	Parmar *et al*., 2022
	Tralokinumab	Neutralizes IL-13, reducing skin inflammation and barrier dysfunction	Moderate-to-severe AD, IL-13-driven inflammation	Injection site reactions, conjunctivitis, and upper respiratory infections	Blair, 2022
	Lebrikizumab	Blocks IL-13 signaling, decreasing inflammation and allergic response	Under investigation for moderate-to-severe AD	Injection site reactions, under further evaluation	Bernardo *et al*., 2023
JAK Inhibitors	JAK1 Inhibitors (Upadacitinib and Abrocitinib)	Selectively inhibits JAK1 to reduce inflammatory cytokine signaling	Moderate-to-severe AD, unresponsive to biologics	Headache, acne, increased risk of infection, and increased blood creatine level	Nogueira and Torres, 2021; Kamata and Tada, 2023
	JAK1/2 Inhibitor (Baricitinib)	Inhibits JAK/2-mediated cytokine signaling to modulate immune and inflammatory responses	Moderate-to-severe AD, used off-label in some regions	Infections, nasopharyngitis, headache, and increased blood creatine level	Nogueira and Torres, 2021; Kamata and Tada, 2023
Antimetabolites	Methotrexate	Inhibits dihydrofolate reductase, reducing DNA synthesis and immune cell proliferation	Severe AD requiring immunosuppression; off-label use	Hepatotoxicity, bone marrow suppression, and nausea	Nedelcu *et al*., 2019
	Azathioprine	Inhibits purine synthesis, suppressing immune system activation	Severe AD with inadequate response to other treatments	Isolated cytopenia, bone marrow suppression, hepatotoxicity, and nausea	Bracho-Borro *et al*., 2022
	Cyclosporine	Inhibits calcineurin-mediated dephosphorylation of the nuclear factor of activated T cells (NFAT), suppressing T cell activation and cytokine production	Moderate to short-term use in severe AD due to nephrotoxicity risks	Nephrotoxicity, hypertension, convulsion, and increased infection risk	Shin *et al*., 2019; Wißfeld *et al*., 2024
	Mycophenolate mofetil	Blocks purine synthesis, impairing T and B cell proliferation	Used in severe AD when other immunosuppressants fail	Increased infection risk, gastrointestinal issues, and leukopenia	Ritter and Pirofski, 2009
Systemic corticosteroids		Suppresses systemic inflammation by broadly inhibiting immune cell activity	Severe chronic AD with no other treatment options; short-term use only	Weight gain, decreased bone density, hyperglycemia, adrenal suppression, and increased infection risk	Poetker and Reh, 2010

tions of IL-4, IL-5, IL-13, IL-31, IL-22, and TSLP, which contribute to the pathogenesis of AD (Bao *et al*., 2013). JAK inhibitors inhibit JAK signaling, thereby blunting inflammation-related cytokine signaling. JAK inhibitors differ in safety, degree of inhibition, and selectivity. Previous clinical studies have shown that topical JAK inhibitors reduce the severity of rashes and relieve itching caused by AD. The reported side effects include folliculitis, acne, and Kaposi's varicelliform eruptions (Papp *et al*., 2021).

Topical ruxolitinib 1.5% cream, a potent selective JAK1/2 inhibitor, was approved by the FDA in 2021 for short-term and discontinuous chronic treatment in patients with mild-to-moderate AD aged 12 years and older (Kim *et al*., 2020). It should not be applied on more than 20% of the body surface area and should only be used in doses up to 60 g per week (Papp *et al*., 2021). This reduces systemic absorption, thereby preventing side effects such as serious infections, lymphoma, major cardiovascular events, and thrombosis. Another JAK inhibitor, topical delgocitinib ointment, inhibits the entire JAK family, including JAK1, JAK2, JAK3, and TYK2, and has been approved in Japan in 2020 for use in patients aged 2 years and older (Nakagawa *et al*., 2020). A phase 2a trial evaluating topical tofacitinib (TOFA) 2% ointment in mild-to-moderate AD demonstrated a significant improvement in the Eczema Area and Severity Index (EASI), with an 81.7% reduction compared with 29.9% in the vehicle group after 4 weeks (Bissonnette *et al*., 2016). Although topical TOFA is not advancing commercially, these findings support the continued development of topical JAK inhibitors as effective treatments for mild-to-moderate AD.

Phosphodiesterase-4 inhibitors

Elevated phosphodiesterase-4 (PDE4) activity has been observed in mononuclear cells of patients with AD. Studies have demonstrated that the topical application of PDE4 inhibitors provides clinical benefits in the management of AD (Markova *et al*., 2007). PDE4 inhibitors are nonsteroidal anti-inflammatory drugs that regulate inflammatory responses while preserving skin integrity. Unlike corticosteroids, they help prevent skin atrophy and epithelial barrier deterioration, making them a valuable alternative for AD treatment (Kucharekova *et al*., 2003).

Crisabolol 2%, a topical PDE-4 inhibitor approved by the FDA in 2016 for the treatment of AD, is indicated for mild-to-moderate disease and is used as an alternative to TCS and TCIs. It is currently approved for use in patients aged >2 years in the United States, European Union, Canada, Australia, Israel, and Hong Kong, but has not yet been approved in Korea (Fujita *et al*., 2021). By blocking PDE, it stops the breakdown of cAMP and reduces overall inflammation (Yang *et al*., 2019). Several clinical trials targeting adult patients with AD have demonstrated its efficacy in significantly improving dermatitis and itching (Hoy, 2017). Meta-analyses have shown that PDE-4 inhibitors such as crisabolol are safer than TCS (Martín-Santiago *et al*., 2022). Common side effects include burns and pain at the application site; however, serious side effects are rare. It appears to be effective when applied to thin skin areas, such as the face, constricted areas, and genitals, and can be used in cases where TCS cannot be used due to their side effects (Zane *et al*., 2016). However, owing to its high cost and similar effects, it is recommended as a second-line treatment (McDowell and Olin, 2019).

Systemic therapies

Systemic therapies are primarily classified into phototherapy and pharmacotherapy. Phototherapy is used to treat various dermatological conditions, including atopy and psoriasis, and has been employed for the management of AD for several decades. However, in recent years, biologics and JAK inhibitors have been approved for use in adults with AD, and there have been a limited number of up-to-date high-quality randomized controlled trials (RCTs) on phototherapy. Furthermore, the accessibility of UV phototherapy is limited, as it requires two to three treatments per week for a duration of 10 to 14 weeks (Davis *et al*., 2024). This section focuses on pharmacotherapy and provides an in-depth evaluation of monoclonal antibodies (mAbs), JAK inhibitors, antimetabolites, and systemic corticosteroids, the use of which is generally limited to short-term treatment in severe or refractory cases owing to the associated risks.

Monoclonal antibodies

Since the 1960s, antibodies have been studied in the context of several autoimmune diseases. OKT3 was the first antibody used to reduce acute rejection in organ transplant candidates. Despite its subsequent withdrawal from the market, numerous mAbs have been developed for the treatment of various neoplastic diseases (Shepard *et al*., 2017). The mAb market has changed rapidly over the past five years; it has doubled in size, becoming dominated by fully human molecules, launching bispecific molecules, and facing competition from biosimilars (Grilo and Mantalaris, 2019).

Monoclonal antibodies are designed to target specific immune pathways involved in disease pathogenesis. The IL-4R pathway plays a key role in the development of allergic inflammation. The IL-4R complex is a heterodimer of IL-4Rα, and IL-4Rs are of particular importance as their ligands. IL-4 and IL-13, are known to mediate allergic responses by promoting TH2 differentiation. There are two pathways related to IL-4R. Type 1 IL-4R is predominantly expressed in hematopoietic cells. The γc chain is paired with IL-4Rα and exhibits exclusive affinity for IL-4R. Type 2 IL-4R is a complex of IL-13Rα and IL-4R and is expressed in both hematopoietic and non-hematopoietic cells. IL-13Rα1 has a low affinity for IL-13 under typical circumstances. However, after forming a complex with IL-4Rα, it gains a high affinity for both IL-4 and IL-13. Initially, atopic drugs, including dupilumab and tralokinumab, were developed to target these pathways (Harb and Chatila, 2020) as well as lebrikizumab which directly inhibits IL-13. While IL-13 and IL-31 are therapeutic targets of monoclonal antibodies, they may also function as biomarkers of disease activity due to their correlation with symptom severity (Gorelick *et al*., 2025). This dual role underscores the importance of understanding molecular functions both from a therapeutic and diagnostic perspective.

Dupilumab: Dupilumab, which is the first effective mAb licensed for AD treatment, is a drug targeting IL-4Rα (Davis *et al*., 2024). The release of pro-inflammatory cytokines, chemokines, and IgE triggered by IL-4 and IL-13 is inhibited. Dupilumab inhibits IL-4 and IL-13 signaling by binding to the IL-4Rα subunit (Harb and Chatila, 2020). It downregulates the inflammatory response associated with TH2 cells in several allergic diseases, including AD and asthma (Del Rosso, 2019).

In 2017, dupilumab was approved by the FDA for the treat-

ment of AD. In South Korea, the Ministry of Food and Drug Safety granted approval in 2018 for its use in adult patients with AD aged 18 years and older. The FDA recognizes dupilumab as a first-line treatment for adults and also prefers its use as a first-line option in special populations, including elderly patients and those with renal disease, liver disease, viral hepatitis, HIV, or a history of cancer (Drucker *et al*., 2022).

The standard dosing regimen for dupilumab consists of an initial subcutaneous injection of 600 mg, followed by 300 mg every two weeks (AAD Guidelines, 2023; Drucker *et al*., 2024). In a large-scale 52-week RCT conducted on adult patients, dupilumab significantly improved atopic symptoms and the quality of life compared to placebo. Clinical trials have established a five-year safety record, with serious safety concerns rarely reported (Blauvelt *et al*., 2017). Despite the development of new medications, dupilumab remains the first-line treatment for AD (Drucker *et al*., 2024).

Tralokinumab: Tralokinumab, an IgG4 human mAb, binds with high affinity to IL-13 and prevents its interaction with IL-13 receptors. By neutralizing IL-13, it reduces inflammation and alleviates symptoms. It is the second AD medication that has been approved, and its efficacy and safety have been verified in several clinical trials (Paller *et al*., 2023a). In a 12-week phase 2b trial, tralokinumab combined with TCS demonstrated early and sustained efficacy and safety in patients with moderate-to-severe AD (Wollenberg *et al*., 2021a). Tralokinumab is administered subcutaneously at an initial dose of 600 mg, followed by 300 mg every two weeks. It has been approved by the FDA in 2021, and in Korea in 2023 (Armario-Hita *et al*., 2023).

Lebrikizumab: Lebrikizumab is a high-affinity IgG4 mAb that selectively targets soluble IL-13 and exhibits strong potency and a slow dissociation rate. It inhibits IL-13 signaling by preventing the formation of the IL-4Rα–IL-13Rα1 heterodimer complex, without affecting IL-4 signaling. Unlike other inhibitors, lebrikizumab does not block IL-13 binding to IL-13Rα2 (a decoy receptor), allowing IL-13 to be internalized into the cell. IL-13 is a key cytokine in AD, and its serum levels are directly correlated with disease severity (Gonçalves *et al*., 2021). Results from a phase 2b multicenter randomized clinical trial (Guttman-Yassky *et al*., 2020) and earlier phase 2b studies (Simpson *et al*., 2018) validated the key role of IL-13 signaling in AD pathogenesis and emphasized the need for further research. Moreover, during the induction phase of two phase 3 clinical trials, 16 weeks of lebrikizumab treatment was effective in adolescents and adults with moderate-to-severe AD (Silverberg *et al*., 2023).

Tralokinumab and lebrikizumab have different mechanisms of action and binding affinities to IL-13 receptors Lebrikizumab selectively inhibits the formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex by blocking IL-13 binding to IL-13Rα1, while still allowing interaction with the decoy receptor IL-13Rα2. In contrast, tralokinumab binds to IL-13 in a way that prevents its interaction with both IL-13Rα1 and IL-13Rα2, thereby fully neutralizing IL-13 signaling and decoy receptor binding. Both show comparable efficacy in moderate to severe AD with favorable safety profiles.

JAK inhibitors

The JAK-STAT pathway is comprised of four JAK kinases and seven STATs. When a cytokine binds to its receptor, it initiates a signaling cascade that leads to JAK activation. Receptor phosphorylation results in the formation of dimeric STATs that regulate the transcription of target genes. It is considered a therapeutic target for various diseases, including AD, Crohn's disease, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis (Mohamed *et al*., 2024). JAK inhibitors are among the most effective systemic treatments for AD; however, they carry the highest risk of adverse effects. Their efficacy varies depending on the specific drug and is dose-dependent. The oral JAK inhibitors abrocitinib (JAK1-selective), upadacitinib (JAK1-selective), and baricitinib (JAK1/2) have been approved for the treatment of AD.

JAK1 inhibitors (upadacitinib and abrocitinib): Upadacitinib and abrocitinib are reversible selective JAK1 inhibitors. As a competitive inhibitor of ATP binding to JAK1, it prevents the phosphorylation and subsequent dimerization of STATs. This inhibition suppresses the transcription and activation of genes involved in inflammatory pathways (Mohamed *et al*., 2024). Upadacitinib has been recognized for its safety and efficacy in clinical trials involving both adults and adolescents with moderate-to-severe AD. Doses of 15 and 30 mg resulted in significant improvements in the eczema area and EASI for up to 16 weeks (Paller *et al*., 2023b). Furthermore, a meta-analysis comparing JAK-STAT inhibitors (upadacitinib, abrocitinib, and baricitinib) suggests upadacitinib 30 mg as the preferred choice for treating AD (Wan *et al*., 2022). Abrocitinib has been approved in two doses: 100 mg and 200 mg. The 200 mg dose demonstrated greater efficacy in reducing itching than dupilumab (Bieber *et al*., 2021).

JAK1/2 inhibitor (baricitinib): Baricitinib exhibits a high affinity for JAK1 and JAK2 and has been approved for AD in Europe. The US FDA has approved baricitinib for immune-mediated diseases but not for atopic skin conditions; however, it is currently used off-label for AD in the US. In a phase 3 monotherapy clinical trial assessing its long-term efficacy over 68 weeks in patients with moderate-to-severe AD, the EASI-75 response rate for the 4 mg dose was 70.0% at 16 weeks and 55.7% at 68 weeks, whereas the 2 mg dose scored 74.1% at 16 weeks and 81.5% at 68 weeks. These findings indicate that both the 2 mg and 4 mg doses have sustained long-term therapeutic effects on AD (Silverberg *et al*., 2021). In a clinical trial involving pediatric patients aged 2 to 18 years, the combination of 4 mg baricitinib and TCS significantly improved sleep onset and reduced TCS use, showing a statistically significant improvement compared to placebo (Torrelo *et al*., 2023). In Korea, baricitinib was approved for the treatment of adult patients with moderate-to-severe active rheumatoid arthritis in 2018 and those with AD in 2022.

Among the three JAK inhibitors, upadacitinib demonstrates the highest short-term efficacy, though it is associated with the highest risk of adverse events. Abrocitinib shows comparable efficacy to upadacitinib and delivers rapid itch relief, but safety concerns remain. Baricitinib, despite being effective, has a slower onset and lower overall efficacy, which may be attributed to its dual JAK1/JAK2 inhibition.

Antimetabolites

Methotrexate: Methotrexate (MTX) is an antifolate metabolite that inhibits DNA, RNA, and purine synthesis. Addition-

ally, its immunomodulatory properties are believed to involve T cell suppression (Calabrese *et al*., 2022). MTX exerts its immunosuppressive effects through multiple mechanisms. It inhibits 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase/inosine monophosphate (IMP) cyclohydrolase, leading to AICAR accumulation and increased adenosine release, which suppresses inflammatory and immune responses by binding to adenosine receptors. Moreover, MTX inhibits dihydrofolate reductase (DHFR), preventing the conversion of dihydrobiopterin to tetrahydrobiopterin, thereby enhancing T cell apoptosis and reducing immune activation. It also activates the adenosine receptor A2a and inhibits NF-κB, a key regulator of pro-inflammatory signaling. Furthermore, MTX upregulates p21, a molecule involved in immune and inflammatory regulation, which contributes to its anti-inflammatory properties. By modulating cell-specific signaling pathways, MTX suppresses pro-inflammatory activity in immune cells, making it a widely used medication for autoimmune and inflammatory diseases, including rheumatoid arthritis and AD (Cronstein and Aune, 2020).

In adults, MTX is initially administered at a dose of 5-15 mg per week, with a maximum weekly dose of 25 mg. However, MTX has not received FDA approval for the treatment of AD, and no clinical trials have exclusively evaluated its efficacy and safety in AD. Nonetheless, in a 12-week study comparing MTX and azathioprine in patients with severe atopic eczema, the SCORAD scores decreased by 42% with MTX and 39% with azathioprine, whereas the EASI scores dropped to 17.4 and 17.2, respectively, showing similar efficacy between the two treatments (Schram *et al*., 2011). These results indicate that MTX provides a short-term improvement with an acceptable safety profile, supporting its use in the treatment of severe atopic eczema. However, major adverse effects associated with MTX include hepatotoxicity, bone marrow suppression, and aplastic anemia, necessitating careful monitoring.

Azathioprine: Azathioprine (AZA) is a synthetic purine analog derived from 6-mercaptopurine (6-MP). AZA was introduced in the 1950s as an immunosuppressant and is used in organ transplantation and autoimmune diseases. It is used to treat chronic inflammatory skin diseases, such as cutaneous lupus, AD, and secondary cutaneous rheumatism. In the body, AZA is metabolized into 6-MP by thiopurine methyltransferase (TPMT). 6-MP is further converted into 6-thioguanine nucleotide (6-TGN) by hypoxanthine-guanine phosphoribosyl transferase. 6-TGN disrupts purine metabolism, leading to the inhibition of DNA and RNA synthesis, ultimately suppressing cell proliferation. Additionally, 6-TGN modulates the immune response by inhibiting the function of T and B cells, thereby reducing autoimmune and inflammatory activities (Bracho-Borro *et al*., 2022). AZA is prescribed to patients with severe AD or those who do not respond to other treatments. The oral dosage is 2.5 mg per day, whereas the injectable doses are adjusted according to the TPMT enzyme activity. Patients with heterozygous TPMT activity receive 1.0 mg/kg per day, whereas those with normal TPMT activity are administered 2.5 mg/kg per day to optimize efficacy and minimize toxicity (AAD Guidelines, 2023; Drucker *et al*., 2024).

Cyclosporine: Cyclosporine is a calcineurin inhibitor that binds to cyclophilin to form a complex that inhibits calcineurin activity. Calcineurin is an enzyme that dephosphorylates a transcription factor called NFAT, which regulates cytokine transcription. As cyclosporine inhibits the activation of NFAT, the gene expression of IL-2 is suppressed, which reduces immune rejection during organ transplantation. In an open-label RCT conducted over 24 weeks, 78.26% of patients who received cyclosporine achieved EASI-75 (Vyas *et al*., 2023). Cyclosporine has demonstrated efficacy in treating moderate-to-severe AD. However, common adverse effects such as nephrotoxicity, hypertension, tremors, headache, paresthesia, hirsutism, gingival hyperplasia, gastrointestinal symptoms, hypertriglyceridemia, and increased susceptibility to infection have been reported (Drucker *et al*., 2020; Siegels *et al*., 2021). Reduction of cyclosporine doses has been proposed as an optimal strategy to enable long-term use while minimizing adverse effects (Kim *et al*., 2023).

Mycophenolate mofetil: Mycophenolate mofetil (MMF) is an immunosuppressant that inhibits inosine monophosphate dehydrogenase (IMPDH), thereby disrupting purine biosynthesis. IMPDH catalyzes the conversion of IMP to xanthosine monophosphate, a key step in purine synthesis. MMF also inhibits guanosine synthesis by targeting this enzyme. Unlike other cells, which have compensatory pathways to bypass this inhibition, B and T cells depend on the *de novo* synthesis pathway to create guanosine nucleotides. Hence, MMF selectively inhibits the proliferation of these immune cells (Allison and Eugui, 2000).

Currently, MMF is approved by the FDA only for preventing organ transplant rejection and is used as an off-label systemic treatment for moderate-to-severe AD. A meta-analysis of the efficacy of MMF indicated that it had a therapeutic benefit in 77% of AD cases and improved SCORAD scores in 38.3% of the patients. MMF is available in oral suspensions, capsules, and tablets, and is administered twice daily. It is generally well-tolerated, with nausea, vomiting, and abdominal cramping being the most frequently reported side effects. However, prolonged treatment is associated with a significantly increased risk of herpes infections. Consequently, MMF is currently recommended as an alternative treatment for individuals who cannot tolerate or experience side effects from other systemic immunosuppressants (Phan and Smith, 2020).

SYSTEMIC CORTICOSTEROIDS

Despite recommendations against their use in clinical practice guidelines, systemic corticosteroids are the only FDA-approved oral immunosuppressants commonly used to treat moderate-to-severe AD (Chovatiya and Paller, 2021). While systemic corticosteroids are frequently prescribed, they are not the sole oral immunosuppressants utilized. Cyclosporine, for instance, is used off-label for treating inflammatory skin disorders such as AD. Although not approved by the U.S. FDA for this indication, it is authorized for AD treatment in other jurisdictions like the European Union (Davis *et al*., 2024). The routine use of systemic corticosteroids for AD is associated with low-certainty evidence, and long-term use is not recommended. Aside from their side effects, severe flare-ups often occur once the systemic corticosteroid is discontinued. It may be used rarely for limited periods in certain cases of severe AD when there are no other treatment options or as a bridge to other long-term treatments (Drucker *et al*., 2018).

BIOMARKER-DRIVEN TREATMENTS FOR AD

While current therapies such as dupilumab and JAK inhibitors effectively target the Th2 pathway, these treatments do not fully address the complex and multifaceted immune dysregulation observed in all patients with AD. Despite the conventional treatments being effective in many patients, there is an unmet need for more targeted therapies that consider the distinct immunological profiles of individual patients. There is growing emphasis on identifying and targeting novel biomarkers that represent alternative immune pathways involved in AD pathogenesis. These biomarkers, summarized in Table 2, have the potential to improve patient outcomes by enabling more precise treatment strategies that reflect the unique disease characteristics of each patient. Recent research has increasingly focused on exploring new therapeutic targets to support the shift toward individualized care and examining their potential to transform the current landscape of AD treatment.

THERAPEUTIC BIOMARKERS FOR AD

Therapeutic biomarkers serve as indicators of disease activity, treatment response, or stratification potential. In AD, a wide range of cytokines, chemokines, and immunoglobulins have been studied as biomarkers. Notably, elevated levels of IL-22 and IL-31 are associated with chronic and pruritic manifestations of AD (Hofbauer *et al*., 2012; Laska *et al*., 2024). IgE and IgG subclasses such as IgG1 and IgG4 have been examined for their roles in immune modulation and disease progression (Shamji *et al*., 2021). TARC (CCL17) is a chemokine increasingly used in clinical practice to monitor therapeutic response, especially in biologic-treated patients (Kataoka, 2025).

Tumor necrosis factor receptor superfamily member 4

Tumor necrosis factor receptor superfamily member 4, also known as OX40, is a co-stimulatory molecule expressed on effector and regulatory T cells and plays a crucial role in the survival, expansion, and differentiation of these cells. OX40L, its ligand, is expressed on antigen-presenting cells and endothelial cells and promotes pro-inflammatory T cell responses. The OX40-OX40L interaction is a critical factor in the pathogenesis of AD and has emerged as a significant therapeutic target in moderate-to-severe AD (Sadrolashrafi *et al*., 2024). It is essential for enhancing effector T cell expansion and prolonging their survival by inhibiting apoptosis, boosting cytokine production, and facilitating the development of T helper memory cells. Naïve T cells are initially activated by antigen-presenting cells through interactions between co-stimulatory molecules, such as CD80/CD86 and CD28. Once activated, the expansion of effector Th1 and Th2 cells is sustained through OX40-OX40L signaling. Although resting memory T cells do not express OX40, upon reactivation, they differentiate into effector memory T cells and start expressing OX40, which further supports their proliferation and function through OX40-OX40L engagement. Preclinical studies have indicated that OX40-OX40L signaling regulates IL-22 production in T cells (Furue and Furue, 2021b).

Rocatinlimab (AMG 451) and amlitelimab (KY1005) are novel therapies targeting OX40 and OX40L, respectively. Rocatinlimab, an immunoglobulin G1 (IgG1) anti-OX40 monoclonal antibody, was evaluated in a phase 2b randomized, placebo-controlled clinical trial. At week 16, patients treated with rocatinlimab showed significantly reduced EASI scores, with clinical responses maintained for up to 20 weeks post-treatment. Rocatinlimab is currently being evaluated in placebo-controlled double-blind trials and open-label phase 3 studies in adolescents and adults with moderate-to-severe AD to further assess its efficacy, safety, and tolerability as a novel therapy (NCT05633355, NCT05651711, NCT05398445, NCT05899816, NCT05724199, NCT05882877, and NCT05704738) (Sadrolashrafi *et al*., 2024).

Amlitelimab is a non-depleting IgG4 human anti-OX40L monoclonal antibody that targets OX40L and hinders interactions with OX40, inhibiting the activation of T cell-mediated inflammation. It demonstrated significant efficacy in a phase 2a clinical trial, with patients showing improvement within two weeks and sustained responses for up to 24 weeks. Amlitelimab is currently undergoing placebo-controlled, double-blind phase 3 clinical trials (NCT06181435 and NCT06130566) to evaluate its efficacy, safety, and tolerability in adults with moderate-to-severe AD (Lé and Torres, 2022).

Another humanized anti-OX40 monoclonal antibody, telazorlimab, has the potential to selectively deplete activated T cells, thereby modulating immune responses and disrupting inflammatory pathways associated with AD. These therapies hold promise for sustained disease control, and ongoing clinical trials are currently evaluating their long-term efficacy and safety. In a phase 2b clinical trial (NCT03568162), telazorlimab demonstrated significant efficacy in reducing EASI scores in adults with moderate-to-severe AD, particularly in high-dose treatment groups. The treatment was well tolerated, with similar rates of adverse events between the telazorlimab-treated and placebo groups; however, no ongoing phase 3 trials are currently investigating its use in AD management (Rewerska *et al*., 2024).

Immunoglobulin E

For a long time, IgE has represented a well-known biomarker of allergic diseases and is elevated in many patients with AD due to increased inflammatory infiltration (Prakash *et al*., 2020). IgE binds to immune cells via high-affinity IgE receptors, which vary depending on the presence or absence of a beta chain. This interaction functions both as an effector mechanism, triggering the release of chemical mediators, and as a regulator of cytokine production, contributing to the inflammatory response in AD (Nunomura *et al*., 2005). The role of IgE in mediating allergic responses, particularly through mast cells and basophils, makes it a key therapeutic target in AD (Karagiannis *et al*., 2013).

Omalizumab, an anti-IgE monoclonal antibody, was evaluated in the Atopic Dermatitis Anti-IgE Pediatric Trial, a 24-week single-center, double-blind, placebo-controlled randomized clinical trial. This study, conducted at Guy's and St. Thomas' Hospital and King's College London, demonstrated a significant reduction in the SCORAD index among children with severe AD treated with omalizumab, confirming its potential to modulate IgE-driven inflammation in AD (Chan *et al*., 2020). The inhibition of IgE binding and subsequent prevention of mast cell and basophil activation in the allergic cascade are the therapeutic mechanisms underlying the use of omalizumab in atopic diseases, including allergic asthma and AD.

Table 2. Therapeutic and diagnostic biomarkers for atopic dermatitis

Type	Biomarker	Role in Atopic Dermatitis	Potential Therapeutic Use	References
Therapeutic Biomarkers	Tumor Necrosis Factor Receptor Superfamily Member 4 (OX40)	Binding of OX40 to its ligand promotes T cell expansion, effector function development, and subsequent memory T cell formation, which drives local and systemic inflammation of AD	Targeted by OX40 inhibitors such as rocatinlimab (anti-OX40 mAb), amlitelimab, and telazorlimab (anti-OX40L mAbs)	Croft *et al*., 2024; Sadrolashrafi *et al*., 2024
	Immunoglobulin E (IgE)	Binding of multivalent allergens to allergen-specific IgEs on sensitized effector cells triggers and mediates allergic inflammation	Target for anti-IgE monoclonal antibodies (omalizumab and ligelizumab)	Chan *et al*., 2020
	Interleukin-5 (IL-5)	Most potent activator of eosinophils, linked to inflammation and asthma comorbidities	Therapeutic target for anti-IL-5 monoclonal antibodies (mepolizumab and benralizumab)	Nagase *et al*., 2020; Gevaert *et al*., 2022
	Interleukin-31 (IL-31)	Binding of IL-31 to its receptor on sensory neurons stimulates the nerve, causing pruritus; also involved in skin barrier dysfunction and inflammation	Targeted by nemolizumab (anti-IL-31R mAb) for pruritus control	Kabashima and Irie, 2021
	Interleukin-22 (IL-22)	Contributes to epidermal thickening and inflammation; involved in chronic AD	Target for fezakinumab (anti-IL-22 mAb) in epidermal repair	Laska *et al*., 2024
	Thymic Stromal Lymphopoietin (TSLP)	Initiates Th2 inflammation; key therapeutic target in allergic diseases	Therapeutic target for tezepelumab (anti-TSLP mAb)	Ebina-Shibuya and Leonard, 2023
Diagnostic Biomarkers	Thymus and Activation-Regulated Chemokine (TARC/CCL17)	Correlates with AD severity; used for disease activity monitoring	Used in monitoring response to dupilumab and tralokinumab	Kataoka, 2014; Kishi *et al*., 2023
	Macrophage-Derived Chemokine (MDC/CCL22)	Associated with Th2 inflammation; helps stratify patients for targeted treatments	May predict effectiveness of IL-4/IL-13 inhibitors (dupilumab and tralokinumab)	Tollenaere *et al*., 2021
	Filaggrin (FLG) Mutations	Key genetic factor affecting skin barrier function; useful for identifying intrinsic AD	Filaggrin-targeted therapies under investigation	Campofelice *et al*., 2019; Dębińska, 2021
	Sphingosine-1-Phosphate (S1P)	Linked to AD severity; potential marker for disease progression	Being explored as a biomarker for JAK inhibitor efficacy; Phase 2 trial presented etrasimod as a systemic treatment (NCT04162769) targeting S1P receptors	Japtok *et al*., 2014; Yamamura and Nakahara, 2022
	CXCL2 (Th17-related cytokine)	Predicts response to Dupilumab; helps in treatment selection	Helps guide selection of IL-4/IL-13 inhibitors	Glickman *et al*., 2020

As the only currently available anti-IgE mAb, over 15 years of clinical experience have been accumulated for omalizumab with more than 1.3 million patient-years of exposure (Wollenberg *et al*., 2021b).

Ligelizumab, a high-affinity anti-IgE antibody, was assessed in phase 2 multicenter, double-blind, placebo-controlled trial. Although the study did not show significant superiority over placebo in terms of the EASI 50 response, patients with higher baseline IgE levels exhibited better treatment outcomes (Bangert *et al*., 2023).

Interleukin-5

It is well known that IL-5 is essential for the growth, differentiation, and survival of eosinophils, which often show increased levels in patients with AD. Increased IL-5 expression promotes eosinophil chemotaxis, facilitating their migration to inflammatory sites. Additionally, IL-5 prolongs eosinophil survival, which is clinically significant as it contributes to the onset and progression of skin inflammation and tissue damage in AD, making IL-5 a potential therapeutic target. Several monoclonal antibodies targeting IL-5 (e.g., mepolizumab and reslizumab) or the IL-5 receptor (e.g., benralizumab) have been developed and are currently under investigation for the treatment of allergic diseases, including AD (Tenero *et al*., 2020).

Mepolizumab is a monoclonal antibody that targets IL-5 and blocks its interaction with its receptor, thereby suppressing eosinophil activity (Garcia *et al*., 2013). In a randomized placebo-controlled parallel-group study involving patients with moderate-to-severe AD, mepolizumab significantly reduced peripheral blood eosinophil counts but did not result in any clinical improvement in AD symptoms. Mepolizumab may be more effective in maintaining disease stability and preventing flare-ups in patients with AD rather than in managing active disease symptoms (Kang *et al*., 2020).

Benralizumab, another anti-IL-5 monoclonal antibody, was tested in the HILLIER trial (phase 2), a 52-week randomized, double-blind, placebo-controlled trial. Unfortunately, the trial was terminated early owing to a lack of efficacy, indicating that targeting eosinophils alone may not be sufficient in treating AD (Guttman-Yassky *et al*., 2023). In contrast, in a randomized placebo-controlled study of patients with moderate-to-severe AD, benralizumab significantly reduced eosinophil counts in both the blood (p<.0001) and allergen-challenged skin (p<.05) while also decreasing the number of mast cells, basophils, and eosinophil progenitor cells. Furthermore, it reduced the blood levels of hematopoietic progenitor cells and type 2 innate lymphoid cells (p<.05), highlighting its role in modulating immune responses. Despite the trend toward improvement in the early cutaneous response (p=.095), benralizumab did not significantly affect the late-phase cutaneous reaction or the size of the allergen-induced skin wheal (Whetstone *et al*., 2024).

Interleukin-31

Being closely associated with pruritus in AD, IL-31 acts on sensory neurons to promote itching. IL-31 binds to its receptors in the peripheral skin, triggering inflammatory cell recruitment and altering the skin microbiome. IL-31 also impairs the epidermal barrier function by reducing the expression of barrier proteins and activating sensory nerves, thereby contributing to itch signal transmission. Elevated IL-31 expression has been detected in both the lesional and non-lesional skin of patients with AD (Hofbauer *et al*., 2012; Szegedi *et al*., 2012). Additionally, IL-31-expressing T cells are more prevalent in lesional skin, further implicating IL-31 in AD pathogenesis (Szegedi *et al*., 2012). Moreover, serum IL-31 levels are strongly correlated with disease severity in patients with AD (Raap *et al*., 2012). Therefore, IL-31 and its receptor have emerged as promising therapeutic targets for pruritic diseases, including AD. Anti-IL-31RA antibodies, such as nemolizumab, have demonstrated potential efficacy in clinical trials (Furue and Furue, 2021a).

Nemolizumab, an anti-IL-31 receptor monoclonal antibody, blocks the IL-31 signaling pathway, thereby reducing itching and skin inflammation in AD. Several clinical trials have demonstrated its efficacy. In a 16-week double-blind phase 3 trial, nemolizumab significantly reduced pruritus scores in patients with moderate-to-severe AD (Labib *et al*., 2022). Additionally, a phase 2b multicenter, double-blind, placebo-controlled trial demonstrated that nemolizumab improved the EASI and pruritus scores, making it a promising treatment option for AD-related itching (Kabashima *et al*., 2020; Silverberg *et al*., 2020). Most recently, findings from the ARCADIA 1 and ARCADIA 2 phase 3 trials confirmed that nemolizumab in combination with topical therapy led to significant improvements in pruritus, EASI scores, and sleep disturbance in adolescents and adults with moderate-to-severe AD, further establishing its clinical utility as a promising treatment option (Silverberg *et al*., 2024).

Interleukin-22

Known for promoting keratinocyte proliferation and inhibiting skin barrier function, IL-22 is a cytokine produced by Th22 cells. It plays a role in exacerbating pruritus by inducing the expression of gastrin-releasing peptide (GRP), a neuropeptide involved in mediating itch sensation, and by upregulating the expression of the GRP receptor on keratinocytes, further augmenting the itch response. Elevated IL-22 levels have been observed in patients with AD, particularly in those with more severe disease (Laska *et al*., 2024).

Fezakinumab is a human IgG1-lambda mAb that directly binds to IL-22 and prevents formation of the IL-22/IL-22 receptor complex. A randomized, double-blind, placebo-controlled phase 2a trial demonstrated significant efficacy and tolerability of fezakinumab in the treatment of AD. The study also demonstrated that fezakinumab significantly improved SCORAD scores in patients with severe AD, particularly those with high baseline IL-22 levels (Guttman-Yassky *et al*., 2018). The same researchers conducted a study evaluating the cellular and molecular effects of IL-22 blockade in moderate-to-severe AD, demonstrating that fezakinumab led to a greater reversal of the AD genomic profile compared to placebo, particularly in patients with high baseline IL-22 expression, who showed significant transcriptomic improvements. The study showed that fezakinumab suppressed multiple inflammatory pathways (Th1, Th2, Th17, and Th22) while upregulating immunoregulatory cytokines (IL-34 and IL-37), showing potential as a targeted AD treatment. However, variability in patient responses suggests a need for predictive biomarkers to optimize therapy (Brunner *et al*., 2019). By targeting IL-22, fezakinumab addresses a key aspect of AD pathogenesis related to epidermal hyperplasia and barrier dysfunction (Laska *et al*., 2024).

Thymic stromal lymphopoietin

The epithelial cell-derived cytokine TSLP plays a pivotal

role in initiating the Th2 immune response in AD. TSLP activates dendritic cells, which then promotes the differentiation of naïve T cells into Th2 cells, thereby driving allergic inflammation. Genetic polymorphisms and high TSLP levels are associated with an increased risk of developing AD. TSLP is highly upregulated in keratinocytes within the lesional skin of patients with acute and chronic AD. In addition, serum TSLP levels are higher in adults with AD than in children with AD and are correlated with disease severity (Luo *et al*., 2023).

Tezepelumab is a mAb that targets TSLP by binding to its receptor, thereby disrupting TSLP-receptor interactions and ultimately inhibiting downstream inflammatory signaling pathways. Tezepelumab has undergone phase 1 (NCT00757042) and phase 2a (NCT02525094) randomized double-blind placebo-controlled clinical trials involving patients with AD were conducted. In phase 2a trial, tezepelumab did not achieve statistical significance in terms of the primary endpoint (EASI 50). However, patients treated with tezepelumab demonstrated improvements in eczema severity and pruritus by week 16, indicating that TSLP inhibition may still offer therapeutic benefits in AD management (Simpson *et al*., 2019).

DIAGNOSTIC BIOMARKERS

Diagnostic biomarkers play a critical role in AD management due to the highly heterogeneous nature of the disease. AD presents in various clinical phenotypes, making it difficult to rely solely on clinical assessments for accurate diagnosis and treatment decisions. The use of diagnostic biomarkers allows clinicians to identify patients with active disease, differentiate AD from other inflammatory skin conditions, and stratify patients according to disease severity or subtype. These biomarkers are also essential for predicting disease progression and developing personalized treatment approaches. By enabling a more precise diagnosis and classification of AD subtypes, diagnostic biomarkers support the shift toward personalized medicine, where treatments are tailored to individual patients rather than using a one-size-fits-all approach.

Thymus and activation-regulated chemokine

Thymus and activation-regulated chemokine (TARC/CCL17) is constitutively expressed in the thymus and is secreted by dendritic cells (DCs), endothelial cells, keratinocytes, and fibroblasts. It is classified as a Th2-associated chemokine owing to its ability to bind to CCR4 (Saeki and Tamaki, 2006). AD is considered a Th2-dominant inflammatory skin disease, especially in its acute phase; hence, TARC/CCL17 is one of the most reliable biomarkers for AD diagnosis, strongly correlating with disease severity. It is used to monitor disease activity and distinguish AD from other inflammatory skin conditions, making it a valuable diagnostic tool (Morita *et al*., 2010). TARC levels are especially useful in patients receiving dupilumab or tralokinumab because reductions in TARC levels can indicate response to these IL-4 and IL-13 inhibitors (Kishi *et al*., 2023). In contrast, nemolizumab, an IL-31 receptor A (IL31RA) antibody, has demonstrated efficacy in reducing AD-related pruritus but may increase serum TARC levels. Clinical trials have shown that TARC elevation does not correlate with changes in EASI scores (Kabashima *et al*., 2020). However, in some patients, nemolizumab use has been linked to severe new-onset or worsening dermatitis, accompanied by abnormally high TARC levels, which may necessitate TCS intensification or discontinuation of nemolizumab treatment (Kataoka, 2025).

Macrophage-derived chemokine CCL22

Macrophage-derived chemokine CCL22 (MDC/CCL22) is a CC chemokine that acts as a strong chemoattractant for monocytes, monocyte-derived DCs, and natural killer cells (Kakinuma *et al*., 2002). Research has consistently demonstrated that the Th2 cytokine-producing cells that infiltrate the skin play a crucial role in the initiation and amplification of atopic skin inflammation. The recruitment of inflammatory cells to the skin is largely regulated by Th2-associated chemokines (Pivarcsi and Homey, 2005). CCL22 is elevated in patients with AD and is associated with Th2 inflammation, making it a useful diagnostic marker for identifying patients with active disease and stratifying them for targeted treatments (Nakazato *et al*., 2008). CCL22 can also help predict the efficacy of dupilumab and tralokinumab because these drugs target Th2-related inflammation (Tollenaere *et al*., 2021).

Filaggrin mutations

Filaggrin (FLG) mutations are a well-known risk factor for AD, particularly intrinsic AD. These mutations compromise the skin barrier and are often considered in diagnostic evaluations to differentiate between intrinsic and extrinsic AD. Individuals with FLG mutations are four times more likely to develop AD than those without mutations. Furthermore, FLG mutations are associated not only with an increased risk of AD but also with greater disease severity (Brown *et al*., 2009). Therefore, therapeutic approaches aimed at inhibiting cytokine-induced FLG suppression or boosting FLG expression may be effective in managing AD. A potential gene-based approach for FLG replacement involves the use of “read-through” drugs, which target mutant alleles by bypassing nonsense FLG mutations during RNA splicing or incorporating amino acids at the mutation site. These drugs are currently under investigation for other genetic disorders and are showing promising results (Campofelice *et al*., 2019). Another strategy focuses on enhancing FLG expression by modulating genetic regulatory elements and promoters of healthy alleles. Although these approaches hold potential, there are currently no available therapies that directly address the reduced FLG protein production caused by genetic variations (Dębińska, 2021). However, filaggrin-deficient patients may benefit from barrier repair therapies, such as emollients and moisturizers.

Sphingosine-1-phosphate

Sphingolipids play crucial roles in the mammalian epidermis and serve both structural and regulatory functions. Keratinocytes produce and release large quantities of ceramide precursors into the extracellular domain of the stratum corneum, where they are further metabolized into specific ceramide species. The proper organization of these ceramides into lipid lamellae is essential for maintaining the epidermal barrier. In addition to their structural roles, sphingolipids also regulate epidermal cell function. Sphingosine-1-phosphate (S1P) is a key signaling molecule that controls vital processes in keratinocytes and skin dendritic cells by inhibiting keratinocyte proliferation while promoting differentiation. S1P also regulates antigen uptake, migration, and cytokine production in dendritic cells. Dysregulated sphingolipid metabolism has been implicated in inflammatory skin diseases including AD (Japtok *et*

al., 2014). Elevated serum levels of this lipid mediator are associated with the severity of AD, making it a potential diagnostic marker for disease activity and progression. S1P receptors (S1PRs) can also be targeted by JAK inhibitors, which modulate immune pathways involved in AD. In addition, a phase 2 clinical trial (NCT04162769) has demonstrated the safety and efficacy of systemic treatment with etrasimod, which targets S1PR1, S1PR4, and S1PR5, in patients with moderate-to-severe AD. These findings pave the way for its advancement to phase 3 studies.

CXCL2 (Th17-related chemokine)

Primarily responsible for producing IL-17, Th17 cells are linked to the pathogenesis of several autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and psoriasis (Sugaya, 2020). The proportion of IL-17-producing CD4+ T cells in peripheral blood is increased in patients with AD and is correlated with disease severity. CXCL2 is closely linked to Th17 cells because IL-17, the key cytokine produced by Th17 cells, triggers keratinocytes to secrete CXCL2, which subsequently attracts neutrophils to inflammation sites (Koga *et al*., 2008). CXCL2 levels have been found to predict response to dupilumab, a biological agent commonly used in AD. High baseline levels of CXCL2 are associated with better outcomes in patients treated with this IL-4/IL-13 inhibitor (Glickman *et al*., 2020).

CONCLUSION

Significant advancements have been made in the treatment of AD with the emergence of targeted biologics and small-molecule inhibitors, revolutionizing disease management. Although conventional therapies remain the foundation of treatment, newer approaches focusing on biomarker-driven precision medicine offer personalized and more effective therapeutic strategies. This review underscores a paradigm shift in atopic dermatitis management, from symptom-driven care to biomarker-guided, precision-based strategies. Advances in immunological research have identified a range of therapeutic biomarkers such as OX40, IgE, IL-5, IL-31, IL-22, and TSLP, which serve as promising targets for next-generation biologics. In parallel, diagnostic biomarkers including TARC/CCL17, MDC/CCL2, filaggrin, sphingosine-1-phosphate, and CXCL2 have emerged as valuable tools for assessing disease severity, monitoring treatment response, and refining patient stratification. These molecular markers reflect the underlying heterogeneity of AD and pave the way for more tailored therapeutic regimens. The integration of these biomarkers into clinical decision-making not only enhances treatment precision but also fosters early intervention and better long-term disease control. Future therapeutic innovations should focus on validating these biomarkers across diverse populations, incorporating them into standardized diagnostic protocols, and identifying novel immunomodulatory pathways. Combining systemic and topical therapies, exploring new immunomodulatory targets, and refining the long-term safety profiles of emerging drugs are critical aspects in the advancement of AD treatment. As research continues to bridge the gap between disease mechanisms and therapeutic solutions, the integration of personalized medicine, predictive biomarkers, and innovative treatment modalities will shape the future of AD management, ensuring more sustainable and effective long-term disease control.

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