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Review Article

Systemic immunomodulatory therapies in severe atopic dermatitis: a comprehensive review of mechanisms, efficacy and long-term management stratagems

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ABSTRACT

Severe atopic dermatitis (AD) represents a complex, chronic inflammatory dermatosis characterized by a profoundly debilitating course, significant comorbid burden and a substantial deterioration in quality of life. The pathophysiological paradigm has evolved beyond a purely T-helper 2 (Th2)-centric model to incorporate a broader spectrum of immune dysregulation, including roles for Th22, Th17 and IL-31-driven pathways, alongside crucial epithelial barrier dysfunction mediated by filaggrin and other structural protein deficiencies. This shift has catalyzed the development and clinical deployment of novel, targeted systemic agents that move beyond traditional immunosuppressants. This exhaustive review synthesizes contemporary evidence from recent clinical trials, real-world efficacy studies and international consensus guidelines to critically appraise the current therapeutic arsenal. We provide a detailed analysis of the pharmacodynamics, clinical trial data and safety profiles for biologic agents such as dupilumab, tralokinumab and lebrikizumab, which selectively inhibit key interleukins. Furthermore, we examine the emerging role of Janus kinase (JAK) inhibitors, including abrocitinib, upadacitinib and baricitinib, focusing on their rapid onset of action and the nuanced risk-benefit calculus mandated by their safety advisories. The review also contextualizes the enduring, though carefully circumscribed, role of conventional systemic immunosuppressants like cyclosporine, methotrexate and mycophenolate mofetil in the modern treatment algorithm. Particular emphasis is placed on therapeutic sequencing, combination approaches, management of secondary infections and strategies for long-term disease control while mitigating adverse effects. The concluding synthesis projects future directions, including combination biologic therapy and personalized medicine approaches guided by endotypic stratification, underscoring the transformative nature of current systemic treatments in altering the disease trajectory for patients with severe atopic dermatitis.

Keywords: Atopic dermatitis, Severe systemic therapy, Biologics, Dupilumab, JAK inhibitors, Interleukin antagonists, Immunomodulation, Treatment guidelines, Real-world evidence, Precision dermatology

INTRODUCTION

Atopic dermatitis is a relapsing, pruritic, eczematous dermatosis whose severe manifestations inflict a multidimensional burden, encompassing intense pruritus, cutaneous pain, sleep disruption and a pronounced elevation in the risk of psychiatric and systemic inflammatory comorbidities. The historical management of severe disease recalcitrant to topical corticosteroids and phototherapy long relied upon a limited portfolio of broad-spectrum immunosuppressive agents, whose utility was frequently constrained by suboptimal efficacy, variable tolerability and concerning long-term toxicity profiles. The contemporary understanding of AD pathogenesis, however, has been refined through advanced molecular profiling, revealing an intricate cytokine network where interleukin (IL)-4, IL-13 and IL-31 are preeminent, though not exclusive, drivers of inflammation, barrier dysfunction and neurosensory pathology. This granular pathophysiological insight has fundamentally reoriented therapeutic development toward precision-based interventions.[1-3]

The last decade has witnessed a paradigmatic shift with the regulatory approval and integration of targeted systemic therapies, inaugurating a new era characterized by improved efficacy and a more favorable safety trajectory. Nevertheless, the rapid proliferation of therapeutic options from monoclonal antibodies against IL-4Rα and IL-13 to orally administered JAK inhibitors introduce novel clinical challenges. These include the formulation of evidence-based treatment algorithms, the appropriate positioning of each agent within a sequential or combinatorial strategy, vigilant monitoring for class-specific adverse events and the long-term management of a chronic condition now viewed as potentially modifiable. This comprehensive review aims to assimilate the most current clinical data from sources such as the journal of the American academy of dermatology, British journal of dermatology and the new England journal of medicine, along with recent meta-analyses and consensus statements from the American academy of dermatology and the European academy of dermatology and venereology. We endeavor to provide a critical, clinically oriented synthesis that elucidates the present and future landscape of systemic intervention for severe atopic dermatitis, thereby equipping practitioners to navigate this complex and dynamically evolving therapeutic domain.[3-5]

Atopic dermatitis stands as one of the most prevalent and burdensome chronic inflammatory skin diseases globally, with its severe phenotypic variant imposing a disproportionate share of the condition's morbidity and healthcare resource utilization. Historically conceptualized as a disorder rooted in cutaneous barrier dysfunction and allergic sensitization, the pathophysiological framework has undergone a profound revision. Contemporary research now delineates a complex, self-perpetuating interplay between epidermal barrier impairment, most notably through loss-of-function mutations in the filaggrin gene and a polarized, dysregulated immune response. This immunologic axis extends far beyond the traditional T-helper 2 (Th2) paradigm, which implicates interleukin (IL)-4, IL-5 and IL-13. Current models incorporate significant contributions from T-helper 22 (Th22) cells and their cytokine IL-22, driving epidermal hyperplasia, and from IL-31, a potent pruritogen directly linking inflammation with the debilitating symptom of itch. Furthermore, variable involvement of T-helper 17 (Th17) and T-helper 1 (Th1) pathways, particularly in chronic, lichenified lesions, adds another layer of heterogeneity to the disease's molecular signature. This intricate cytokine milieu not only sustains inflammation but also directly inhibits the synthesis of critical barrier proteins, thereby creating a vicious cycle that perpetuates disease activity and severity.[5,6]

The clinical consequence of this pathophysiology is a disease state characterized by extensive eczematous lesions, profound and often intractable pruritus and a high frequency of secondary bacterial and viral infections, predominantly with staphylococcus aureus and herpes simplex virus. The impact transcends dermatologic boundaries, correlating strongly with a spectrum of systemic atopic and inflammatory comorbidities, including asthma, allergic rhinitis, eosinophilic esophagitis and a heightened risk for cardiovascular and neuropsychiatric diseases. The assessment of disease severity itself has evolved, moving beyond purely physician-reported measures like the eczema area and Severity index (EASI) to incorporate validated patient-reported outcomes that capture the lived experience of itch, sleep disturbance and the detrimental effects on quality of life. It is within this context of a severe, systemic, and multifaceted disease that the limitations of conventional therapy become starkly apparent.[5,6]

For decades, the management of severe atopic dermatitis refractory to optimized topical therapy and phototherapy was confined to a narrow suite of non-specific systemic immunosuppressants. Agents such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil, while offering relief for some patients, were hampered by a well-documented profile of off-target adverse effects, including renal toxicity, hepatotoxicity, myelosuppression and increased risks of infection and malignancy with long-term use. Their mechanisms of action, broadly suppressing T-cell activation or proliferation, lacked specificity for the AD inflammatory cascade, leading to variable efficacy and a frequent need for dose adjustments or discontinuation due to toxicity. Consequently, a significant and urgent unmet need persisted for therapies with targeted mechanisms, superior safety profiles and predictable, sustained efficacy.[7,8]

The translation of bench-side discoveries regarding AD pathogenesis into clinical therapeutics has fundamentally

altered this landscape. The advent of biologic agents, exemplified by the IL-4Rα antagonist dupilumab, demonstrated for the first time that selective cytokine blockade could achieve unprecedented levels of disease control while maintaining a favorable safety trajectory. This success validated the central role of the IL-4 and IL-13 pathways and catalyzed the development of a second generation of biologics targeting IL-13 alone (tralokinumab, lebrikizumab) and other mediators. Concurrently, the emergence of Janus kinase (JAK) inhibitors, small molecules that intracellularly block signaling downstream of multiple cytokine receptors, offered a potent oral alternative with rapid onset of action. However, the pharmacologic promiscuity of JAK inhibitors, while conferring broad efficacy, has also introduced complex safety considerations, including class-based warnings regarding thromboembolic events, major adverse cardiovascular events and malignancy, necessitating sophisticated risk stratification and monitoring protocols.[9]

Thus, the current therapeutic arena for severe atopic dermatitis is both promising and complex, characterized by an expanding arsenal of targeted therapies with distinct mechanisms, efficacy profiles, and safety considerations. This evolution mandates a critical synthesis of the latest evidence to inform rational clinical decision-making. A comprehensive understanding must now integrate data from pivotal phase III clinical trials, longitudinal extension studies, and the increasingly vital insights from real-world evidence, which captures outcomes in more heterogeneous patient populations outside strict trial protocols. Furthermore, the development of international consensus guidelines, such as those from the American academy of dermatology and the European task force on atopic dermatitis, strives to provide a structured framework for therapy selection and sequencing. This review's background underscores the necessity of navigating this new paradigm, where treatment is no longer merely about suppression but about strategic, pathophysiology-informed intervention aimed at altering the long-term course of severe atopic dermatitis.[9]

CLINICAL MANIFESTATIONS AND DISEASE BURDEN IN SEVERE ATOPIC DERMATITIS

The clinical phenotype of severe atopic dermatitis represents a profound and often debilitating culmination of the underlying pathophysiological processes, extending far beyond the classic presentation of childhood eczema. Its manifestations are heterogeneous, dynamic, and frequently involve multiple organ systems, reflecting the systemic nature of the inflammatory dysregulation. Cutaneously, the hallmark is the presence of extensive eczematous lesions, often covering more than 10% of the body surface area, with a morphology that evolves with chronicity. In the acute phase, lesions are characterized by intensely pruritic, erythematous papules and vesicles on a background of ill-defined erythema, frequently accompanied by serous exudate and crusting, indicative of significant barrier disruption and inflammation. Subacute lesions present with erythematous, scaly plaques, while the chronic phase is dominated by lichenification a leathery thickening of the skin with accentuated skin markings as well as fibrotic papules (prurigo nodularis) and fissuring. This lichenification is a direct consequence of the chronic mechanical trauma from incessant scratching and rubbing, driven by the unremitting pruritus, which itself is now understood to be a neuroimmunological phenomenon mediated by cytokines such as IL-31 and thymic stromal lymphopoietin (TSLP).[10,11]

The distribution of lesions in adults often follows a distinctive pattern, preferentially affecting the flexural areas (antecubital and popliteal fossae), the face and neck (including troublesome periocular dermatitis) and the hands, although severe disease can become generalized, involving the trunk and extremities in a widespread, confluent manner. Cutaneous dyspigmentation, both post-inflammatory hyperpigmentation and hypopigmentation, is a common sequela, contributing to long-term stigmatization and psychological distress. A critical and frequent complication is the colonization and overt infection of the compromised skin barrier, most notably by staphylococcus aureus, which exacerbates inflammation through superantigen production. Patients with severe AD also face an increased susceptibility to disseminated viral infections, such as eczema herpeticum (caused by herpes simplex virus), which can be life-threatening and necessitates immediate therapeutic intervention.[11]

However, the impact of severe atopic dermatitis is not confined to the integumentary system. The disease imposes an immense systemic and psychosocial burden. The cardinal symptom of pruritus is typically severe, intractable, and worst at night, leading to catastrophic sleep fragmentation. This chronic sleep deprivation cascades into daytime fatigue, impaired cognitive function, and significant reductions in work and school productivity. The visibility of the lesions, coupled with the social stigma of a "skin condition," often leads to social withdrawal, anxiety and depression, with studies confirming a markedly elevated prevalence of these psychiatric comorbidities compared to the general population.[12]

Furthermore, severe AD is increasingly recognized as a systemic inflammatory disorder with clear atopic and non-atopic march trajectories. There is a robust epidemiologic link with other type 2 inflammatory conditions, including asthma, allergic rhinitis and eosinophilic esophagitis, suggesting shared underlying mechanisms. More recent data also point to associations with broader systemic inflammation, potentially contributing to an elevated risk of cardiovascular diseases, such as hypertension and myocardial infarction, independent of traditional risk factors. This expanded

view reframes severe atopic dermatitis not as an isolated dermatosis but as a cutaneous marker of a pervasive inflammatory state. The profound and multidimensional burden of the disease encompassing physical discomfort, relentless pruritus, sleep disruption, psychiatric morbidity and systemic comorbidity underscore the critical imperative for effective, systemic therapeutic interventions capable of modulating this complex pathophysiology and altering the disease trajectory. This comprehensive burden of illness forms the essential clinical rationale for the deployment of advanced systemic immunomodulatory therapies, which aim not only to clear the skin but to mitigate this broader spectrum of suffering.[12]

DIAGNOSTIC CRITERIA AND ASSESSMENT OF SEVERITY IN SEVERE ATOPIC DERMATITIS: FOUNDATIONS FOR SYSTEMIC INTERVENTION

The accurate diagnosis and comprehensive assessment of severe atopic dermatitis constitute a critical prerequisite for the appropriate initiation of systemic immunomodulatory therapy. The diagnostic process is fundamentally clinical, relying on the recognition of a constellation of characteristic features rather than a single pathognomonic test. Established sets of diagnostic criteria, most notably those proposed by Hanifin and Rajka, provide a structured framework, integrating major and minor clinical features. Essential major criteria include the presence of pruritus, a classic morphology and distribution of eczematous lesions (often with age-specific patterns), a chronic or chronically relapsing course, and a personal or family history of atopy. These are supported by a multitude of minor criteria encompassing xerosis, ichthyosis, palmar hyperlinearity, keratosis pilaris, immediate skin test reactivity, elevated serum IgE levels, early age of onset, and a susceptibility to cutaneous infections, among others. While the Hanifin and Rajka criteria remain a foundational reference, their complexity in routine practice has led to the adoption of more streamlined criteria, such as those from the UK Working Party, which offer a pragmatic diagnostic algorithm suitable for both clinical and epidemiological settings.[12]

A critical step in the diagnostic journey is the meticulous exclusion of a broad differential diagnosis, a process that necessitates clinical acumen and at times, histopathological corroboration. Conditions that can mimic severe atopic dermatitis include other forms of dermatitis such as allergic contact dermatitis, seborrheic dermatitis, and stasis dermatitis, as well as primary immunodeficiencies like hyper-IgE syndrome (Job syndrome) and Wiskott-Aldrich syndrome. Cutaneous T-cell lymphoma, specifically mycosis fungoides in its early stages, can present with eczematous plaques and must be ruled out, particularly in cases of adult-onset or treatment-refractory disease. Other considerations include psoriasis, scabies, dermatophytosis and metabolic disorders like acrodermatitis enteropathica. A thorough patient history, detailed physical examination and judicious use of patch testing or skin biopsy are indispensable tools in this discriminative process. Histopathological examination, while rarely required for typical cases, reveals features such as spongiotic dermatitis, acanthosis and a perivascular infiltrate of lymphocytes and eosinophils, findings that, while supportive, are not exclusive to AD and must be interpreted within the clinical context.[12]

Beyond establishing the diagnosis, the rigorous quantification of disease severity is paramount for guiding therapeutic decisions, particularly the transition to systemic agents.

Severity assessment in atopic dermatitis has evolved into a multidimensional construct, moving beyond pure physician-reported measures of skin involvement. The eczema area and severity index (EASI) score stands as the gold standard objective tool in clinical trials, providing a validated, region-weighted assessment of erythema, induration/papulation, excoriation, and lichenification across four body regions. Its counterpart for more rapid clinical use is the validated Investigator's Global assessment (vIGA), a static, 5-point scale. However, the profound burden of AD is not fully captured by lesion morphology alone. Consequently, contemporary assessment mandates the integration of patient-reported outcomes (PROs) that quantify the subjective experience of the disease. The peak pruritus numerical rating scale (PP-NRS) and the dermatology life quality index (DLQI) or the AD-specific atopic dermatitis control tool (ADCT) are now considered essential components of a holistic evaluation.

The concept of "severe" disease, therefore, is operationalized as a combination of high objective scores (e.g., EASI >21), significant body surface area involvement, failure or inadequacy of response to optimized topical therapy with potent corticosteroids and/or topical calcineurin inhibitors, and a severe impact on quality of life and sleep as reflected in PROs.[12,13] This comprehensive diagnostic and evaluative approach confirming the diagnosis, excluding mimickers and objectively quantifying both cutaneous signs and patient-centric symptoms forms the essential bedrock upon which the decision to escalate therapy to systemic agents is made.

It ensures that the significant benefits and potential risks of advanced therapies are reserved for the patient population with truly severe, recalcitrant disease, aligning with the principles of precision medicine and responsible pharmacotherapy outlined in current international guidelines. Furthermore, establishing this robust baseline allows for the accurate monitoring of therapeutic response, facilitating data-driven adjustments in management over the long-term course of this chronic condition.[14]

CURRENT THERAPEUTIC PARADIGMS IN THE MANAGEMENT OF SEVERE ATOPIC DERMATITIS

The contemporary management of severe atopic dermatitis is characterized by a dynamic and rapidly evolving therapeutic landscape, fundamentally reshaped by the advent of targeted immunomodulatory agents. This paradigm shift has moved the field beyond a primary reliance on reactive, non-specific immunosuppression towards a more strategic, pathophysiology-informed approach aimed at long-term disease control and an improved safety profile. The foundation of therapy for all patients, including those with severe disease, continues to be stringent, daily skin barrier repair and protection with bland, fragrance-free emollients. This foundational measure, while insufficient as monotherapy for severe AD, remains critical to supporting epidermal barrier function, reducing trans epidermal water loss and providing a degree of symptomatic relief. The traditional first-line pharmacologic intervention consists of potent or super-potent topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs), such as tacrolimus and pimecrolimus, utilized to manage acute flares and maintain control in milder areas. However, in severe atopic dermatitis, defined by extensive body surface area involvement and a profound impact on quality of life, the feasibility and long-term safety of chronic, widespread application of these topical agents are severely limited, necessitating escalation to systemic therapy.[14]

The modern algorithm for systemic therapy is stratified, commencing with conventional systemic immunosuppressants, which continue to hold a significant, though more precisely defined, position. Cyclosporine, a calcineurin inhibitor, is often cited for its rapid onset of efficacy, making it valuable for inducing control in severe, acute flares. However, its utility is constrained by well-documented risks of nephrotoxicity, hypertension and the potential for rebound upon discontinuation, generally limiting its use to short-term courses. Methotrexate, a folate antagonist, and mycophenolate mofetil, an inhibitor of purine synthesis, serve as slower-acting but potentially steroid-sparing options for long-term management. Their use requires vigilant monitoring for hepatotoxicity, myelosuppression, and gastrointestinal intolerance. The role of systemic corticosteroids, while providing rapid and potent anti-inflammatory effects, is now heavily circumscribed due to their severe long-term adverse effect profile and the predictable, often severe, disease rebound following taper. Current international consensus guidelines strongly discourage their chronic or repeated use as maintenance therapy for severe AD, reserving them only for exceptional, brief circumstances.[14]

The true transformation in management has been ushered in by the introduction of targeted biologic therapies and JAK inhibitors. Dupilumab, a fully human monoclonal antibody that inhibits the shared receptor subunit for interleukin-4 (IL-4) and interleukin-13 (IL-13), represents the first-in-class biologic for AD. Its efficacy in achieving significant reductions in the EASI and improving pruritus and quality of life has been robustly demonstrated across multiple phase III trials and sustained in long-term extension studies. Its subcutaneous administration and favorable safety profile, with conjunctivitis being the most notable adverse event, have established it as a cornerstone therapy. Following dupilumab, tralokinumab and lebrikizumab, monoclonal antibodies specifically targeting IL-13, have emerged, offering a nuanced alternative with slightly distinct efficacy profiles, particularly in the domain of pruritus relief, as evidenced by recent head-to-head trials and real-world effectiveness studies.[14]

Concurrently, the class of oral JAK inhibitors, including abrocitinib, upadacitinib, and baricitinib, has introduced a potent, rapidly acting oral alternative. These small molecules function by intracellularly inhibiting the JAK-STAT signaling pathway, thereby blocking the signal transduction of multiple cytokines implicated in AD pathogenesis, including IL-4, IL-13, IL-31 and thymic stromal lymphopoietin (TSLP). Their oral bioavailability and speed of onset, particularly for pruritus relief, are significant advantages. However, their pharmacologic promiscuity necessitates a careful and informed risk-benefit analysis. Post-marketing surveillance data and updated meta-analyses have led regulatory agencies to issue class-wide warnings regarding increased risks of major adverse cardiovascular events, thrombosis, malignancy and serious infections. Consequently, their use is typically guided by strict eligibility criteria, avoidance in high-risk patients and ongoing laboratory and clinical surveillance, as detailed in recent risk mitigation guidelines from dermatologic and rheumatologic societies.[14]

The current therapeutic challenge, therefore, lies not in a lack of options but in the sophisticated art of therapeutic sequencing and personalization. Factors influencing the choice of first-line systemic agent include speed of onset required, patient preference for route of administration (subcutaneous versus oral), comorbid conditions (e.g., history of malignancy or thromboembolic disease), concomitant ocular surface disease and payer access.

Furthermore, the management of severe AD is increasingly recognized as a longitudinal endeavor, requiring proactive strategies for managing partial responders, addressing secondary infections and combining systemic agents with continued topical and non-pharmacologic measures. The integration of patient-reported outcomes into routine clinical assessment is now considered standard practice to ensure treatment aligns with the patient's lived experience of the disease. As the field progresses, ongoing research into biomarkers for treatment response and the exploration of combination therapies, such as biologics with JAK inhibitors or novel agents targeting the IL-33 and TSLP pathways, promise

to further refine and personalize the treatment landscape for this complex and burdensome condition.[15,16]

CONCLUSION

The therapeutic landscape for severe atopic dermatitis has undergone a profound and definitive transformation, moving from an era defined by empirical, broad-spectrum immunosuppression to a new paradigm of precision medicine guided by an increasingly granular understanding of disease pathogenesis. This comprehensive review underscores that the management of severe AD is no longer merely an exercise in symptomatic palliation but a strategic endeavor aimed at fundamentally altering the inflammatory cascade and by extension, the long-term trajectory of the disease. The emergence of targeted biologic therapies, most notably interleukin-4 and interleukin-13 antagonists, has provided a foundational pillar for treatment, offering patients unprecedented levels of disease control with a safety profile that permits sustainable, long-term use. Concurrently, the advent of Janus kinase inhibitors has introduced a potent oral alternative characterized by rapid onset of action, particularly for the debilitating symptom of pruritus, thereby addressing a critical unmet need for swift and meaningful relief. However, the potent mechanism of these agents necessitates a sophisticated and vigilant approach to patient selection and monitoring, informed by evolving real-world evidence and pharmacovigilance data that continue to refine our understanding of their risk-benefit calculus.

The enduring, albeit more narrowly defined, role of conventional systemic immunosuppressants highlights the importance of a graduated and individualized treatment algorithm. These agents remain vital tools, particularly in resource-limited settings or for specific patient subsets, but their use is now optimally framed within a sequential strategy that considers the superior long-term risk profiles of newer agents. Crucially, the objective of contemporary therapy extends beyond cutaneous clearance measured by physician-reported scales. The integration of patient-reported outcomes into routine clinical assessment has rightfully shifted the therapeutic focus toward holistic endpoints: the restoration of sleep, the alleviation of pruritus, the improvement in quality of life and the mitigation of the systemic inflammatory burden that links severe AD to its comorbid conditions. This patient-centric approach is essential for evaluating true therapeutic success.

Looking forward, the frontier of severe AD management lies in the further personalization of care. Current research efforts are intensely focused on identifying reliable clinical and molecular biomarkers capable of predicting response to specific therapeutic classes, a development that would mark a leap towards truly stratified medicine. Furthermore, the exploration of novel therapeutic targets within the cytokine network, such as the IL-33 and TSLP pathways, holds promise for expanding our arsenal. The investigation of rational combination therapies, potentially pairing biologics with JAK inhibitors or other novel agents for synergistic effect in recalcitrant cases, represents another promising avenue. Ultimately, the goal is to evolve from a reactive model of care to a proactive, preventive strategy that not only controls established disease but also modulates the underlying immune dysregulation to prevent flares and complications. The convergence of advanced therapeutics, robust clinical guidelines and a deepened mechanistic understanding position the field to offer transformative care, turning the management of severe atopic dermatitis from a story of chronic burden into one of sustained disease control and restored patient well-being.

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