Opinion

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Monoclonal Antibodies in Severe Atopic Dermatitis: Beyond Dupilumab

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease that affects millions worldwide, imposing a substantial burden on quality of life and healthcare systems. While AD can present with a spectrum of severity, patients with moderate-to-severe disease often suffer from persistent pruritus, sleep disturbance, recurrent skin infections, and psychological comorbidities. Traditionally, treatment options for severe AD were limited to broad immunosuppressants such as cyclosporine, methotrexate, and azathioprine, which provide variable efficacy but are constrained by significant systemic toxicities and long-term safety concerns. The advent of targeted biologic therapies has revolutionized the therapeutic landscape. Dupilumab, an interleukin (IL)-4 receptor α antagonist that blocks IL-4 and IL-13 signaling, became the first monoclonal antibody approved for AD and has transformed disease outcomes for many patients. However, not all patients achieve complete remission with dupilumab, and some experience inadequate responses, partial disease control, or adverse effects such as conjunctivitis. This has catalyzed an intensive search for novel biologics targeting other immune pathways implicated in AD. The following article explores the evolving role of monoclonal antibodies in the treatment of severe atopic dermatitis, highlighting emerging therapies beyond dupilumab, their immunological rationale, clinical trial evidence, and potential to reshape the future of personalized dermatology [1].

Description

One major area of innovation lies in the development of monoclonal antibodies that directly neutralize IL-13, a central cytokine driving barrier dysfunction, inflammation, and fibrosis in AD. Tralokinumab and lebrikizumab are two IL-13 inhibitors that have demonstrated efficacy in phase III clinical trials. Tralokinumab, a fully human monoclonal antibody, binds IL-13 and prevents its interaction with both IL-13Rα1 and IL-13Rα2 receptors. Clinical studies have shown that tralokinumab significantly improves Eczema Area and Severity Index (EASI) scores, reduces pruritus, and enhances quality of life compared to placebo. Both agents highlight the importance of IL-13 as a therapeutic target and provide alternative options for patients unable to tolerate dupilumab [2].

Another cytokine of great interest in AD pathophysiology is IL-31, often termed the “itch cytokine” due to its potent role in pruritus. Elevated IL-31 levels correlate with itch severity in AD patients, and IL-31 signaling through the IL-31 receptor complex on sensory neurons directly activates pruriceptive pathways. Nemolizumab, a monoclonal antibody targeting the IL-31 receptor A, has emerged as a promising therapy to address the unmet need of severe, treatment-resistant pruritus in AD. Clinical trials have shown that nemolizumab rapidly reduces itch intensity, improves sleep disturbance, and enhances patient-reported outcomes, even when skin lesions are only partially improved. By directly targeting the neuronal-immune axis of itch, nemolizumab represents a paradigm shift in AD therapy, providing relief from one of the most distressing symptoms that significantly impairs quality of life [3,4].

Upstream mediators of type 2 inflammation are also attractive therapeutic targets. Epithelial-derived cytokines, including TSLP, IL-25, and IL-33, are alarmins released in response to environmental triggers such as allergens, microbes, and pollutants, and they initiate and amplify Th2 immune responses. Tezepelumab, an anti-TSLP monoclonal antibody, has demonstrated efficacy in asthma and is now being evaluated in AD. Early studies suggest that inhibiting TSLP can dampen the initiation of Th2 inflammation, potentially preventing disease flares and reducing severity. Similarly, antibodies targeting IL-33 (itepekimab) are in development, with the aim of blocking this upstream driver of type 2 and innate lymphoid cell responses. These strategies represent a shift from targeting effector cytokines such as IL-4 and IL-13 to intercepting the initiation of allergic inflammation at its earliest stages. Beyond the Th2 axis, there is growing recognition of the role of Th22 and Th17 cytokines in subsets of AD patients, particularly in certain ethnic populations and in pediatric cases. IL-22 promotes epidermal hyperplasia and barrier dysfunction, while IL-17 contributes to inflammation and antimicrobial peptide regulation. Fezakinumab, an IL-22 blocking antibody, has shown modest efficacy in clinical studies, particularly in patients with severe disease. Similarly, dual inhibition strategies, such as antibodies blocking both IL-17 and IL-22 or combined Th2/Th17 targeting, are being explored to address complex immunological profiles [5].

Conclusion

The therapeutic landscape of severe atopic dermatitis has expanded dramatically beyond dupilumab, with a growing arsenal of monoclonal antibodies targeting IL-13, IL-31, TSLP, IL-33, and other pathways. These agents provide valuable options for patients who do not achieve adequate control with dupilumab and address unmet needs such as refractory pruritus. The diversity of therapeutic targets reflects the complex immunopathology of AD, underscoring the importance of personalized medicine in tailoring treatments to individual immune profiles. While challenges remain in terms of accessibility, cost, and long-term safety data, the progress in biologic therapy marks a transformative era in AD management. By expanding beyond dupilumab, monoclonal antibodies are reshaping the treatment paradigm, offering hope for durable control, improved quality of life, and reduced disease burden for patients with severe atopic dermatitis. Precision medicine approaches leveraging these biomarkers could optimize treatment selection, reduce trial-and-error prescribing, and maximize patient benefit.

Acknowledgement

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Conflict of Interest

None.

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