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Review Article

Lebrikizumab: a novel approach in managing atopic dermatitis in pediatric patients

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ABSTRACT

Atopic dermatitis is a prominent dermatological condition in children that frequently affects their lifestyle. Conventional treatments frequently prove inadequate, necessitating the use of biological agents like Lebrikizumab to address the condition at its core pathophysiological level. The introduction of biologic drugs has broadened the spectrum of treatment options for patients with moderate to severe atopic dermatitis, especially those who have not achieved satisfactory results with conventional monotherapy or combination therapies, or those with contraindications to systemic immunosuppressive agents. Lebrikizumab appears to be a promising option for the treatment of atopic dermatitis, showing a strong response in clinical trials. It offers the potential for improved long-term efficacy and a reduction in adverse effects. This article provides an overview of Lebrikizumab's role in addressing the pathogenesis of atopic dermatitis and highlights its current advancements.

Keywords: Atopic dermatitis, Lebrikizumab, Skin disease, Dermatology, Pediatrics

INTRODUCTION

Atopic dermatitis (AD) is an inflammatory skin condition with a high incidence that typically initiates during early childhood. It is estimated that 15% to 20% of children and 3% of adults receive a diagnosis.[1,2] AD is a chronic, systemic inflammatory skin ailment characterized by persistent itching and eczematous lesions, following a recurrent pattern with symptoms of exacerbation and remission.[3,4] In most cases, AD precedes other atopic comorbidities, such as asthma or allergic rhinitis, a phenomenon known as the atopic march.[5] It can either resolve during childhood or persist into adolescence (5-20%) and adulthood (1-3%).[6] The diagnosis is primarily clinical and relies on the morphological characteristics and distribution of the lesions since, to date, no specific pathological or laboratory findings have been identified for the disease. Therefore, strict adherence to standardized diagnostic criteria is crucial to prevent misdiagnosis.[7]

AD has been found to have a profound impact on quality of life, with alterations in both social and physical functioning. Mental health disorders, such as anxiety, depression, and attention-deficit/hyperactivity disorder, are also more common in both children and adults with AD.[1,4] Up to 20% of AD cases can be classified as moderate or severe according to different clinical measurement scales. The severity of the itch experienced by the patient, the impact the disease has on sleep patterns, and the severity of the itching that the patient experiences must be taken into account.[8,9] Therefore, there is a significant need for more effective treatments to alleviate

symptoms and enhance the quality of life. Understanding the underlying mechanisms of the disease is essential for developing effective treatment strategies. Studies focusing on the pathogenesis of AD have increased in recent years, leading to the introduction of targeted therapies, including IL-4/13 inhibitors, for patients with moderate to severe AD resistant to systemic treatments.[7,10] In this review, we will focus on Lebrikizumab as a targeted therapy, its role in the disease's pathogenesis, and advancements in its development.

METHODS

A digital article search was conducted on PubMed, Google Scholar, and ClinicalKey using the following keywords: "Lebrikizumab," "atopic dermatitis," "atopic dermatitis pathophysiology," and "atopic dermatitis treatment." The search encompassed articles published within the last decade, without language restrictions, and only those meeting quality standards were chosen for review.

PATHOPHYSIOLOGY

AD is a multifactorial and heterogeneous disorder that arises from the interplay of genetic and epigenetic factors, environmental agents, immunological defects in both innate and adaptive immune responses, and dysfunction of the epithelial barrier. The epidermal barrier comprises a matrix of lipids and structural proteins, possessing antimicrobial properties and serving to preserve skin hydration. The skin microbiome plays a pivotal role in the innate immune response of the skin by maintaining immune balance and reducing the colonization of pathogenic bacteria on the skin.[7,11] Various genetic disorders have been identified in cases of AD, with mutations in filaggrin (FGL) being common, present in 10-50% of cases. Filaggrin plays a crucial role in maintaining skin barrier integrity by aiding in keratinocyte formation and regulating water balance, acid pH, and skin barrier function. When filaggrin molecules are decreased or defective, it leads to higher pH, water loss, dryness, and an increased function of kallikrein serine protease (KLK). However, in cases where filaggrin mutation is not present, other alterations have been observed, such as desmoglein-1 (DSG1), corneodesmosin (CDSN), serine protease inhibitor Kazal type 5 (SPINK5), Matt, and lymphoepithelial-related inhibitor Kazal type (LEKTI).[3,6,7]

The immune response is also a significant factor, with the cytokine profile having a substantial impact on keratinocyte life cycles. Keratinocytes express pattern recognition receptors that identify pathogenic antigens, triggering an increase in proinflammatory cytokines. Furthermore, an imbalance between T-helper Th2/Th22 and Th1/Th17 responses leads to alterations in cell-mediated immune responses. This can result in chronic skin lesions, and acute skin lesions may be associated with increased gene expression levels of Th2 interleukins. In AD patients, both IL-4 and IL-13 levels are elevated in the skin and serum, with IL-31 being the first cytokine shown to be directly involved in neuronal pruritus.[3,6,7]

Moreover, cytokines like IL-4 and IL-13 play a role in skin barrier dysfunction and promote an amplified Th2 immune response in the acute phase of AD. These changes involve increased chemokine production, decreased antimicrobial peptides, and intensified allergic inflammation. Skin barrier damage and inflammation can be exacerbated by microbial abnormalities, particularly Staphylococcus aureus (*S. aureus*) overgrowth. IL-13 and IL-4 have been found to reduce antimicrobial peptide (AMP) expression by keratinocytes, increasing susceptibility to S. aureus colonization and infection. Skin barrier damage leads to increased transepidermal water loss and allows for the penetration of potential irritants, allergens, and microorganisms into the skin, which, in turn, enhances the inflammatory immune response. IL-13 and IL-4 also induce itching and contribute to the itch response, primarily through histamine-independent sensory nerve stimulation, either directly or by amplifying the pruritic effects of IL-31. Physical damage caused by scratching further exacerbates skin alterations.[5] Different AD phenotypes are described according to IgE levels (intrinsic and extrinsic), age (pediatric and adult AD), FLG gene mutation, race or ethnicity (Asian and European/ American).[12]

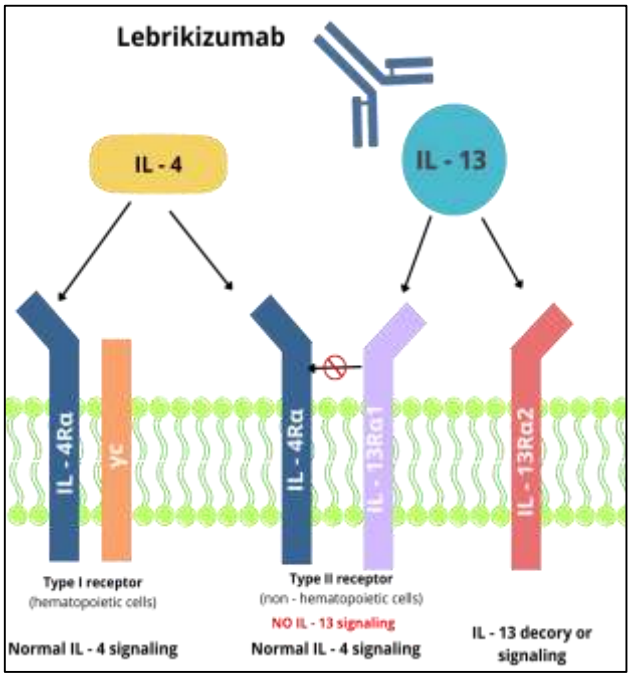

Figure 1: Lebrikizumab mechanism of action.

CONVENTIONAL MANAGEMENT

One of the treatment approaches for atopic dermatitis focuses on reducing scratching, preventing infections resulting from the sensitivity of the stratum corneum, and, most importantly, reducing inflammation. Non-pharmacological therapeutic measures that are essential

for treatment include skin hydration and the elimination of predisposing or exacerbating factors. Educating and raising awareness in families is key to achieving these goals. Proper clinical management should encompass both basic measures and intensification of treatment for severe AD cases.[12,13] To address the varying degrees of atopic dermatitis involvement, mild cases affecting only a limited body surface area can benefit from local treatments, such as topical corticosteroids, calcineurin inhibitors, or phototherapy, in conjunction with proper skincare and regular moisturizing. For patients experiencing sleep disturbances due to itching, an oral antihistamine with a sedative effect, such as diphenhydramine (Benadryl) or hydroxyzine, can be added.[2] However, for individuals with moderate and severe forms of the disease, as well as those who suffer from a decreased quality of life, the aforementioned therapeutic options may prove insufficient.[14] In cases of more advanced disease degrees, systemic therapy becomes necessary. Immunosuppressive drugs like cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil are available, though they are used with caution due to their high toxicity and adverse effects. It's important to note that none of these options directly target the underlying mechanisms of AD.[5]

Biological agents as treatment of atopic dermatitis

Biological agents, also known as biologics or biological therapies, have emerged as promising treatments for atopic dermatitis (AD). Unlike traditional medications, biologics are designed to target specific components of the immune system or inflammatory pathways, offering a more targeted and often effective approach.[8,15] Here's an overview of biological agents for atopic dermatitis: Nemolizumab: Nemolizumab is a monoclonal antibody that targets the IL-31 receptor. IL-31 is a cytokine associated with itching and has been found to be elevated in AD patients. By blocking the IL-31 receptor, nemolizumab helps alleviate itching and improve the overall condition of patients with moderate to severe AD. Dupilumab: Dupilumab is a monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling. These cytokines play a crucial role in the inflammatory processes associated with AD. Dupilumab has been approved for moderate to severe AD in adults and children over the age of 12. It has shown significant efficacy in reducing symptoms and improving the quality of life for patients with AD. Tralokinumab: Tralokinumab is another monoclonal antibody that specifically targets IL-13. By inhibiting IL-13, tralokinumab interferes with the inflammatory response that contributes to AD symptoms. Clinical trials have demonstrated its potential in reducing disease severity and improving itchiness in AD patients. Upadacitinib: Upadacitinib is a Janus kinase (JAK) inhibitor that modulates the immune response by targeting specific signalling pathways. JAK inhibitors have shown promise in various inflammatory conditions, including AD. Upadacitinib is being investigated as a potential treatment for moderate to severe AD. Targeted microbiome transplantation lotion (TMT): contains Staphylococcus hominis, decreases the burden of $^{S.\ aureus}$, however, in a phase 1 trial shows no improvement in dermatitis.[16] Lebrikizumab: it is an mAb that binds to IL-13 but unlike other drugs that bind to IL-13, it shows better qualities, among them: lower adverse effects, greater efficacy and safety.

Lebrikizumab: a promising treatment for atopic dermatitis

Approximately one-third of pediatric patients suffer from moderate to severe AD, necessitating advancements in therapy, including the initiation of systemic treatments.[11] Considering the pivotal role of IL-13 in the Th2 inflammatory response, the selective inhibition of IL-13 holds promise as a viable approach to treating AD.[14] Lebrikizumab is a subcutaneously administered drug functioning as an IL-13 inhibitor. It neutralizes the cytokine and prevents the binding and heterodimerization of IL-13Rα1 and IL-4Rα. Notably, lebrikizumab does not hinder the binding of IL-13 to the decoy receptor IL-13Rα2, which is thought to be involved in regulating endogenous IL-13.[17] While the exact metabolic pathway of lebrikizumab remains underexplored, it is hypothesized to undergo metabolism via proteolytic degradation, similar to endogenous IgG, owing to its status as a humanized IgG4 monoclonal antibody. A minor hinge portion mutation in the molecule enhances the stability of lebrikizumab (Figure 1).[1] The linear pharmacokinetic profile and relatively extended half-life of the drug allow for less frequent dosing, typically every four weeks, and may even reduce the need for more frequent dosing during maintenance. Lebrikizumab treatment has also yielded clinically significant improvements in skin clearance outcomes (assessed through IGA and EASI) over a 52-week treatment period, as evaluated by investigators. Skin improvement has been observed from the initial assessment at week 4, with an increasing percentage of patients experiencing improvements throughout the treatment duration. The positive benefit-risk profile evident in this study provides compelling evidence that targeting IL-13 with lebrikizumab represents a meaningful approach for the treatment of moderate to severe AD in the adolescent population.[18]

Advances in the development of lebrikizumab

Lebrikizumab is currently in experimental phases. In the phase II TREBLE study, Lebrikizumab at a dose of 125 mg administered every 4 weeks demonstrated a significant improvement in all disease severity scores assessed at week 12, with no significant response observed in the single-dose groups. However, it's worth noting that the Lebrikizumab 250 mg single-dose group exhibited numerically higher and earlier responses for better outcomes, suggesting a potential dose-response relationship or even the benefit of a loading dose. In the phase IIb study, Lebrikizumab exhibited a rapid onset of action and dose-dependent efficacy, leading to statistically significant improvements in skin lesions, pruritus, and

quality of life scores by week 16. Notably, a reduction in pruritus severity was observed as early as day 2 in patients receiving the high dose of Lebrikizumab (500 mg).[5]

The results from available phase III trials appear to confirm the effectiveness of Lebrikizumab in treating moderate to severe AD. Data from the ADvocate and ADhere trials highlight Lebrikizumab's potential to reduce the disease burden in patients with uncontrolled AD, whether used alone or in combination with topical corticosteroids (TCS). Clinically significant differences were noted at week 4 for measures of skin clearance, pruritus, and quality of life. By week 16, over 50% of patients receiving Lebrikizumab achieved an EASI 75 response, which increased to 70% when combined with TCS. Additionally, at that point, more than a third of patients in all trials had light or nearly clear skin.[5].

Regarding safety, Lebrikizumab was generally well tolerated, with adverse effects being mild and transient, typically lasting for 1 to 3 days. The most common adverse events included upper respiratory tract infection (2.7–11.3%), nasopharyngitis (2.5-12.0%), headache (1.3-5.3%), pain at the injection site (0.0-5.3%), and injection site reactions (1.3%).[19] Infections reported in ≥1% of patients receiving Lebrikizumab every 2 weeks, excluding eye-related disorders, included nasopharyngitis, oral herpes, and COVID-19. Nasopharyngitis and herpes zoster were reported more frequently in the Lebrikizumab group (4.4% and 0.6%, respectively) compared to the placebo group (3.2% and 0.0%, respectively). While there have been reports of conjunctivitis in patients receiving Lebrikizumab for atopic dermatitis, the rates of conjunctivitis were relatively low in the phase II TREBLE trial (9.6%) and in the Phase IIb trial for various groups (ranging from 0.0% to 3.8%). These rates were lower than those reported in phase II and phase III trials with dupilumab (8.6-22.1%). The exact mechanism behind conjunctivitis in AD patients receiving IL-13 and IL-4-targeting biologics remains unclear, with one theory suggesting that inhibition of IL-13 and IL-4 signalling may disrupt conjunctival goblet cells, crucial for maintaining conjunctival mucosal surface homeostasis, leading to ocular adverse events.[19] Notably, adverse events such as exacerbation of atopic dermatitis and skin infection occurred at a lower incidence among patients receiving Lebrikizumab compared to those on placebo in the trials.[20] These findings suggest that Lebrikizumab may offer a significant advancement in the treatment of AD, providing an effective and safe alternative due to its more direct mechanism of action against the proinflammatory cytokine IL-13.[1] However, it's important to note that as of the time of writing this article in October 2023, the FDA has denied approval of Lebrikizumab. The denial was related to conclusions drawn after inspecting a third-party contract manufacturing organization. It's worth mentioning that the efficacy and safety of the drug were not questioned, and the pharmaceutical company is hopeful of obtaining approval in the coming years.

DISCUSSION

Current data suggests that targeting IL-13 alone may be sufficient for achieving adequate therapeutic responses in AD patients, with fewer side effects. This lends support to the hypothesis that IL-13 plays a pivotal role in the pathogenesis of AD. Lebrikizumab appears to be a promising targeted biological agent for individuals with moderate-to-severe AD.[5] Lebrikizumab has demonstrated success in treating both adults and adolescents. In its two phase 3 randomized, double-blinded clinical trials, 30% to 40% of patients achieved clear or nearly clear skin, in contrast to the 11% to 13% of those receiving a placebo.[5] It's important to note that both tralokinumab and lebrikizumab are associated with injection site reactions and ocular surface disorders.[21] A study assessing the efficacy and safety of combining Lebrikizumab with low to mid-potency topical corticosteroids (TCS) in patients with moderate-to-severe AD showed that the Lebrikizumab+TCS group displayed statistically significant improvements in all key secondary endpoints. Most of the treatment-emergent adverse events (TEAEs) were non-serious, mild, or moderate in severity, and they did not result in the discontinuation of the study.[22] The safety profile of Lebrikizumab remained consistent across trials, whether or not TCS were used and in both adults and children.[23] It's essential to acknowledge that biologics have their limitations. They can be costly, require regular administration via injection or infusion, and may have associated side effects. The long-term safety of these treatments is still being evaluated, and their use in specific patient populations, such as pregnant women and children, requires further investigation.[24]

CONCLUSION

Atopic dermatitis stands as one of the most prevalent skin conditions among infants, affecting over 20% of children in industrialized regions. Notably, 45% of cases manifest before the age of six months, 60% before the first year of life, and a staggering 89% before the age of five. AD exhibits extreme heterogeneity in terms of severity, progression, and clinical features. Nevertheless, it's essential to recognize that there are currently no diagnostic criteria more effective and precise than those of an expert dermatologist for diagnosing AD. Misdiagnosis and delayed treatment can impact not only the physical health of the child but also their psychological well-being. Hence, early identification of AD is critical, allowing for the selection of the most appropriate therapeutic approach based on its severity. The complexity of AD's pathogenesis, the absence of a definitive cure, and the fact that available treatments offer only temporary relief have spurred research efforts to discover a definitive solution for AD. In this context, Lebrikizumab emerges as a promising option for individuals with atopic dermatitis. The introduction of biologic drugs has broadened the spectrum of treatment options for patients with moderate to severe AD, especially those who have not achieved satisfactory results with conventional monotherapy or

combination therapies, or those with contraindications to systemic immunosuppressive agents. Biologics appear to provide a more precise and individualized approach, reducing symptoms, enhancing quality of life, and potentially mitigating the long-term complications associated with uncontrolled AD.

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