International Journal of Multidisciplinary Innovation and Research Methodology (IJMIRM)
ISSN: 2960-2068, Volume 4, Issue 1, January-March, 2025, Available online at: https://ijmirm.com

Lebrikizumab: A Novel Interlukin 13 Monoclonal Antibody

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ABSTRACT

The prevalence of AD in adolescents is estimated at approximately 15% worldwide, with up to 50% suffering from moderate-to-severe disease. The recent treatment approaches to atopic dermatitis are novel mono clonal antibody lebrikizumab. A Lebrikizumab is a novel, high affinity, monoclonal antibody that selectively targets interleukin -13 and prevents formation of the interleukin -13Rα1/ interleukin -4Rα heterodimer receptor signaling complex. Lebrikizumab does not prevent interleukin -13 binding to the interleukin -13Rα2 decoy receptor, which is thought to be involved in endogenous regulation of interleukin-13. Interleukin -13 is the primary upregulated cytokine in atopic dermatitis skin and is the pathogenic mediator driving atopic dermatitis pathophysiology. Lebrikizumab, tralokinumab and cendakimab are therapeutic monoclonal antibodies that target interleukin-13. Lebrikizumab is a potent, neutralizing high-affinity antibody with a slow disassociation rate from interleukin-13. Additionally, lebrikizumab does not interfere with interleukin-13 clearance.

Keywords: Lebrikizumab, Interleukin, Atopic Dermatitis, Antibody.

Running Title: Lebrikizumab: A Novel Monoclonal Antibody.

INTRODUCTION

Atopic dermatitis is a complex disease that is committed by genetic, environmental and immunologic factors [1]. Interleukin-13 is a primary pathogenic inflammatory mediator of atopic dermatitis which drives effects such as a defective skin barrier, dermal inflammation, allergic response and lichenification [2]. Interleukin-13 gene polymorphisms are associated with an increased risk for developing atopic dermatitis. Interleukin-13 can reduce epithelial integrity through the downregulation of filaggrin, loricrin and involucrin, increasing the risk of sensitization to environmental allergens. Additionally, Interleukin-13 can act on keratinocytes to downregulate their differentiation, decrease the production of antimicrobial peptides and induce the production of T-cell Chemo attractants that mediate T-cell infiltration into atopic dermatitis lesions. Interleukin-13 mediated tissue inflammation promotes fibrotic skin remodeling and skin thickening. Finally, Interleukin-13 may also sensitize peripheral sensory neurons that induce pruritus. Interleukin-13 is a cytokine secreted by T helper type 2 cells and natural killer cells, as well as mast cells, basophils, eosinophils and innate lymphoid cell type 2 cells [3].

Current therapeutic approaches for moderate to severe atopic dermatitis in adolescents include regular use of topical emollients and anti-inflammatory agents such as topical corticosteroids, calcineurin inhibitors, and phosphodiesterase-4 inhibitors. The currently approved systemic agents for moderate-to-severe atopic dermatitis include the biologics dupilumab and tralokinumab and the Janus kinase inhibitors upadacitinib, baricitinib, and abrocitinib [4]. Due to the heterogeneity of atopic dermatitis, additional systemic therapy options suitable for long term management of moderate-to-severe atopic dermatitis in adolescents are required [5].

Lebrikizumab is a monoclonal immunoglobulin antibody that specifically binds and neutralizes interleukin -13. Lebrikizumab has an affinity to human interleukin-13 that is 10 pM with an epitope that allows interleukin -13 to bind to interleukin-13Ra1, but inhibits human interleukin -13 signaling through the interleukin -4Ra/ interleukin -13Ra1 receptor complex [6]. Lebrikizumab is in phase 3 development for moderate-to-severe AD. Lebrikizumab is investigational selective antiinterleukin-13 monoclonal antibody which binds to a different epitope than tralokinumab. In a phase 2a proof of concept trial in adults with moderate to severe atopic dermatitis, overall results with lebrikizumab in single doses or once monthly in combination with a topical corticosteroid showed a dose dependent response and generally positive findings on key outcomes. [7] The findings of the phase 2a proof of- concept study 21 informed the design of our phase 2b dose-ranging trial. This article reports results of the randomized clinical trial

assessing the efficacy and safety of lebrikizumab monotherapy every 4 weeks or every 2 weeks in adults with moderate to severe atopic dermatitis. The review extensively focuses the role of interleukin-13 and the most recent data on lebrikizumab in the management of atopic dermatitis.

Pharmacology and Mechanism of Action of Lebrikizumab

Lebrikizumab was first investigated for the treatment of asthma. A meta-analysis of more than 2000 patients that received lebrikizumab for moderate-to-severe asthma aimed to characterize its pharmacokinetics. Lebrikizumab is administered by subcutaneous injection and has consistently shown linear dose-proportional pharmacokinetics, high bioavailability (estimated as 85%), and a half-life of 19–26 days. Lebrikizumab is a humanized IgG monoclonal antibody which binds to soluble interleukin-13 with high affinity to an epitope that does not interfere with its binding to the receptor but instead prevents interleukin-4Rα/IL13Rα1 heterodimerization, therefore blocking downstream signaling. Lebrikizumab does not prevent IL-13 binding to the IL-13Rα2 decoy receptor, therefore allowing it to maintain this putative endogenous regulatory mechanism.[8]

Clinical Efficacy of Lebrikizumab in Atopic dermatitis

The clinical efficacy of the Lebrikizumab has been tested in numerous phase II and phase III clinical trials. TREBLE trial (NCT02340234) was a randomized, placebo controlled, double-blind, phase IIa multicenter trial evaluated the efficacy and safety of lebrikizumab in different regimens as an add-on therapy to topical corticosteroids in adults with moderate to severe forms of atopic dermatitis. All patients were concomitantly treated with medium potency topical corticosteroids twice daily to avoid study dropouts. The primary endpoint, defined as the achievement of a 50% reduction in Eczema Area and Severity Index score from baseline to week 12, was reached in a significantly greater proportion of patients treated with lebrikizumab 125 mg every 4 weeks than those who received placebo (82.4% versus 62.3%; $p = 0.026$), with no statistically significant response in single dose groups. Also, 125 mg every 4-week group had significantly more patients achieving secondary endpoints, including an Eczema Area and Severity Index score 75 responses, a 50% reduction in the SCORAD tool, and an IGA score of 0 (clear) or 1 (almost clear) at week 12. Again, no statistically significant response was seen in single-dose groups at week 12, but the 250 mg single dose group have shown numerically higher and earlier responses in many outcomes evaluated, denoting a possible dose-response relationship. [7]

The phase III trials of the monoclonal antibody were designed to evaluate lebrikizumab as monotherapy in adult and adolescent patients with moderate to severe atopic dermatitis in which the treatment consisted of 16 week induction phase followed by a 36 week maintenance period.[9,10] In both trials, a significantly higher percentage of patients taking lebrikizumab achieved the primary outcome response, defined as an IGA score of 0 or 1, with a reduction of at least 2 points from baseline at week 16 and 33% respectively [10]. Patients receiving lebrikizumab also experienced statistically significant improvements in skin clearance and pruritus, as well as improvements in interference of itch on sleep and quality of life, as measured by key secondary efficacy endpoints. A higher percentage of patients had an Eczema Area and Severity Index 75 response at week 16 in the lebrikizumab group than in the placebo group. In both studies, statistical significance was achieved starting at week 4 for IGA 0/1, Eczema Area and Severity Index 90, and pruritus NRS.[10] Maintenance period from16 to 52 week is based on re-randomization 2:2:1 of responders in the induction period to receive lebrikizumab. Most patients did not require topical rescue therapy, although use was permitted during the maintenance period.[10]

ADhere (NCT04250337) is a 16 week randomized, double-blind, placebo controlled, parallel group, phase III study designed to evaluate the efficacy and safety of lebrikizumab when used in combination with topical corticosteroids treatment, compared with placebo, in combination with topical corticosteroid in adult and adolescent patients with moderate to severe atopic dermatitis. The result of the clinical trial concluded that among patients taking lebrikizumab plus topical corticosteroid, 41% achieved an IGA 0/1 response at week 16 compared with 22% patients taking placebo plus topical corticosteroid at a significant *p value* of = 0.01. Moreover, 70% of patients taking lebrikizumab plus topical corticosteroid achieved an Eczema Area and Severity Index 75 response at week 16, compared with 42% taking placebo plus topical corticosteroid.

Significant differences between patients receiving lebrikizumab with topical corticosteroid and placebo with topical corticosteroid were observed as early as 4 weeks for Eczema Area and Severity Index 75. Patients in the lebrikizumab group also achieved statistically significant improvements across all key secondary endpoints when compared with placebo plus topical corticosteroid, including percentage in Eczema Area and Severity Index score from baseline to 16 week. [11] A study in pediatric population consisted of a 16 week randomized study patients age range from 6 months to 18 years of age is in progress. The study is a double-blind study, which aimed to measure the effect, safety, and pharmacokinetics of lebrikizumab in pediatric participants with moderate to severe atopic dermatitis.[12] Furthermore, the effect of lebrikizumab on vaccine immune responses in adult patients is being investigated in a phase III randomized, double-blind, placebo-controlled trial. [13] The clinical trials investigating lebrikizumab for treatment of atopic dermatitis are still ongoing. [14,15]

Safety report of lebrikizumab

In various clinical trials of lebrikizumab used in the treatment of atopic dermatitis, the various adverse events were observed. Conjunctivitis was reported in 15 patients (9.6%) in the lebrikizumab group, but also in 4 patients (7.5%) in the placebo group. Herpetic infections and peripheral eosinophilia occurred only in lebrikizumab treated patients but were infrequent (3.8% and 3.2%, respectively) and nonserious. All of these eosinophilia related events were asymptomatic.[7] In other clinical trials [9,10] the authors reported upper respiratory tract infections in 7.5%, nasopharyngitis 6.6%, injection site reactions 5.7%, herpes infections 3.5% and conjunctivitis in 2.6% enrolled patients. The phase III clinical trials also showed adverse drug events such as Conjunctivitis (8%), nasopharyngitis (7 to 10%, headache (3% to 6%), herpes infection (5%), injection site reactions (2 to 3%), eosinophilia (1 to 2%). The side effects of various other clinical trials [11] were nearly similar with reported conjunctivitis (5%), headache (5%), herpes infection (3.4%), injection site reactions (2.8%). Most of the adverse effects in clinical trials were reported as mild or moderate in intensity and nonserious and did not lead to treatment discontinuation with lebrikizumab.

Agents specifically targeting interleukin-13, namely tralokinumab and lebrikizumab, emerged
as potential therapeutic alternatives to dupilumab, which antagonizes both interleukin -4 and interleukin -13 signaling. In fact, inhibition of interleukin -13 alone seems to be sufficient to reach adequate therapeutic responses in atopic dermatitis. The results of available phase III trials seem to corroborate effectiveness of lebrikizumab in the treatment of moderate-to-severe AD. Data from various clinical trials [9,10,11] demonstrated the potential for lebrikizumab to reduce disease burden for patients with uncontrolled atopic dermatitis, when used either alone or combined with topical corticosteroids, respectively.

Lebrikizumab demonstrated rapid onset of action. Clinically meaningful differences were observed as early as week 4 for skin clearance, pruritus, and quality of life measures. At week 16, more than 50% of patients receiving lebrikizumab achieved an EASI 75 response, increasing to 70% when combined with topical corticosteroids. Currently, in all trials, more than one third of the patients had clear or almost clear skin [9,10,11].

Furthermore, the results from 52-week clinical trial [10] demonstrated that around 80% of lebrikizumab responders-maintained improvements in skin clearance, disease severity, and pruritus. It was also observed that loss of clinical response following withdrawal of lebrikizumab was slow, with about half of patients re-randomized to placebo still showing clear or almost clear skin at week 52. More than 60% maintained improvement on disease severity and pruritus scores [10]. Across all studies, lebrikizumab-treated patients showed less requirement of rescue medication.

[7,9,10,11] Rapid and consistent in the relief of pruritus is worthy of note efficacy of lebrikizumab, since it is considered the most burdensome symptom among patients with atopic dermatitis.[9] The data obtained provides additional support to the hypothesis that interleukin-13 is a potent enhancer of neuronal responses to several pruritogenic stimuli, which are effectively blocked by lebrikizumab. Lebrikizumab shown to successfully reverse interleukin-13 elicited neuronal itch sensitization and excitability in a dose-dependent fashion, and also shown to downregulate some gene transcriptional changes driven by interleukin -13, exerting significant effects in the first 24 h after administration. Thus, lebrikizumab seems to directly address the interleukin -13-enhanced neuronal itch, which can explain its anti-pruritogenic efficacy in atopic dermatitis patients.[16]

Regarding the safety profile, lebrikizumab seems to be well tolerated in atopic dermatitis patients. The majority of patients experienced none or only mild side effects. The most commonly reported adverse effects were conjunctivitis (2–10%), nasopharyngitis (5–10%), headache (3–6%), and injection site pain.[7,9,10,11] Transient and mild eosinophilia was also noted, but with no clinical implications. These changes are probably related to the decrease of eosinophil trafficking from the blood to the tissues as a result of reduced chemotaxis by inhibiting interleukin-13 activity.[7] The vast majority of adverse effects were nonserious, mild to moderate in intensity, resolved with simple general measures, and did not lead to treatment discontinuation [7,9,10,11]. With the 110 week clinical trial, it is expected that further data on long term efficacy, posology, and safety of lebrikizumab in atopic dermatitis will become available. [17] Clinical trials in the pediatric population are still going on to test the efficacy and safety of lebrikizumab in atopic dermatitis.[12] Current data suggests that targeting interleukin-13 alone may be enough to achieve adequate therapeutic responses in patients with atopic dermatitis, maybe with less side effects, and supports the hypothesis that interleukin -13 is the pivotal cytokine in the pathogenesis of atopic dermatitis.

CONCLUSION

The pathogenesis of the atopic dermatitis demonstrated the involvement of interleukin-13 as a key cytokine. The results of phase II and phase III clinical trials seem to supports the efficacy of the selective interleukin-13 inhibitor lebrikizumab in the treatment of moderate to severe atopic dermatitis along with a considerable safety profile. Based upon the clinical data the lebrikizumab seems to be a promising targeted biological agent for patients with moderate to

severe atopic dermatitis. However, more data on the long-term clinical efficacy and safety, is required to clarify its place in the therapeutic ladder of atopic dermatitis.

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