THE EFFICACY AND SAFETY OF LEBRIKIZUMAB PLUS TOPICAL CORTICOSTEDOIDS IN MODERATETO SEVERE ATOPIC DERMATITIS.

[1]Dr Modepalli Pavan Kumar

[1]Associate Professor, Department of Dermatology, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry - 605502.

Corresponding Author: Dr Modepalli Pavan Kumar

Abstract

Inflammatory and chronic skin conditions such as AD have a serious impact on patients' quality of life. A phase 3 randomised, placebo-controlled trial, ADhere (NCT04250337) examined the efficacy and safety of low-to-mid potency topical corticosteroids (TCSs) that contain IL-13 monoclonal antibody in moderate and severe AD, adolescents, and adults. Combining lebrikizumab and TCS was found to have tremendous effects on skin clearance and itch intensity, sleep disturbances, and quality of life in the trial. There has already been a statistically significant increase in EASI-75 week 4 and IGA (0,1) week 8 responses. Combination therapy was highly compliant and mild or moderate adverse events were reported mainly. In addition, these findings support the use of lebrikizumab and TCS as an effective method of managing moderate and severe AD.

Keywords: Atopic dermatitis, lebrikizumab, topical corticosteroids, phase 3 trial, EASI-75

Introduction

The prevalence of AD in children is 20 percent, whereas the prevalence in adults is 2-7 percent. AD is characterized by severe itching, sleep disorders, and skin discomfort, which affects daily activities, social life, and the quality of life. Adults and adolescents experience AD at different times in their lives, and AD adversely affects their quality of life (QoL). A topical steroid and emollient are the most widely used treatment options for mild AD today. When the condition is moderate to severe, additional systemic therapies and/or phototherapy should be considered. In recent years, several biologic drugs, including dupilumab, tralokinumab, and systemic Janus kinase inhibitors, have been utilized to treat moderate-to-severe AD. Due to AD's heterogeneity, additional treatment opportunities will be required in long-term management. Inflammatory cytokines, such as interleukin-13 (IL-13), are involved in the Th2-mediated immune response. They are the prime cause of AD pathogenesis and its clinical manifestations. In addition to its high binding affinity and specificity of epitopes, lebrikizumab has a high dissociation rate and high affinity of epitopes. Phase 2b data have shown that this is a critical limitation of lebrikizumab for patients with AD. It is not clear, however, whether clinical practice can be directly related to the monotherapy tests. A surprising fact is that topical medications still play an important role in the treatment of moderate-severe AD patients. The addition of lebrikizumab to the topical medications may be a significant contribution to the literature concerning the use of biologics in combination with TCS therapy in the background. It was conducted in a phase 3 phase combination trial comparing lebrikizumab low and mid-potency TCS with TCS for mild to severe AD in adolescents and adults.

Methods

Study Design

An outline of the trial plan can be found in supplement 1. It was a 16 week, multicenter, placeo-controlled, parallel-group, phase 3 randomized, 2-blind, multicenter, 16 week, randomized clinical trial (NCT04250337), which was conducted in 54 outpatient clinics in Germany, Poland, Canada and the United States. It was initiated on February 3, 2020 and ended on September 16, 2021. We have taken into account a database lock date of 16/12/2021 in the current report. Moreover, we determined the

results using basic criteria, which were 16 in Eczema Area and Severity Index (EASI) and 3 in Investigator Global Assessment (IGA) (All the inclusions and CONSORT).

During the trial, the patients receiving topical and systemic treatments were required to cease the treatment at least one week before randomization (see eFigure in Supplement 2). In this study, eligible patients were randomised to receive either lebrikizumab or placebo (ratio 2:1) based upon their geographical location (the US, Europe, and the rest of the world), age (adolescents vs adults), and severity of their disease (IGA of 3 vs 4). A multivariate analysis was conducted on the age, sex, ethnicity and race of patients to investigate the treatment response in relation to their phenotypes. Considering the fact that AD phenotypes are not distributed equally across populations and depend on factors such as age, chronic disease, race, genetic makeup, IgE levels, and molecular processes, the race/ethnicity data was considered. We selected the parameter of race and self-reported ethnicity of patients. We gave patients lebrikizumab in dosages of 500mg in week 0, 250mg in week 2, and 250mg every two weeks (Q2W) over a 16-week period, and a placebo with topical corticosteroids (TCS). Participants are also advised to initiate TCS of AD symptoms with low-mid potency as a baseline test. There is no need to worry about applying TCIs to delicate parts of the body. Depending on the location, low potency or mid potency TCS was applied (hydrocortisone 1% cream or triamcinolone acetonide 0.1% cream). TCS was applied to the patients at their request after they requested not to use TCS or prevent it at their own will. In addition to the TCS and TCIs, the patients' daily activities were documented through an electronic diary. When the clinical condition worsens, high dosages or systemic therapy are applied (oral corticosteroids, phototherapy, or cyclosporine). The patient was to be responsible for attending to the stopped drug and administering all the tests in this scenario. Participants in ADjoin were eligible to join an extension trial (long-term trial) called ADjoin (NCT04392154) if they had previously participated in ADjoin. Those who were prematurely discontinuing a study or who did not receive the extension study after about 12 weeks of the final dosage were assigned numbers by the blinded study medication, and no information was available to anyone involved. Researchers were blinded to the treatment assignment so as to maintain the integrity of the treatee and investigator. As part of the ADhere clinical trial, the Declaration of Helsinki and the Council of International Organizations of Medical Sciences and Good Clinical Practice were adhered to. The ethical principles of informed consent were applied to determine the study's ethics and ensure that all participants gave their informed consent prior to the study beginning. Parents and legal guardians were required to give their consent in writing, and minors had to give their consent in writing.

Efficacy and Safety Assessments

Based on the initial analysis, the efficacy outcome was determined by finding the proportion of patients with an IGA score of 0 or 1 who had declined at least 2 points between baseline and week 16. The primary secondary efficacy outcomes were: percentage of patients with 75 percent improvement in EASI (EASI-75) at week 16 (co-primary endpoint in the European medicines agency); percentage change in EASI total score at week 16; percentage of patients with 90 percent improvement in EASI (EASI-90) at week 16; and percentage of patients with 4-point or greater improvement in the Pruritus NRS at week 16 (a co-primary endpoint The other central secondary endpoint IGA and E The safety measures addressed were adverse events (AEs), serum chemistry, hematology and urinalysis, and physical examination and vital signs. Additionally, lebrikizumab immunogenicity was tested, which detects antibodies. Besides routine safety monitoring, one blinded and unblinded safety study was performed and the results were confirmed by an independent data safety monitoring board after 6 months.

Results

Table 1. Baseline Demographics and Disease Characteristics in the mITT Population.

Population Demographics	No. (%)	PBO + TCS (N=86)	LEB + TCS (N=172)
The average (SD) age, the year		36.8 (18.2)	37.3 (19.5)
The young adolescent (ages 12-18)		18 (20.9)	38 (22.1)
18-year-olds (adults)		68 (79.1)	134 (77.9)
Female		42 (48.8)	83 (48.3)
Race			
Asian		16 (18.6)	23 (13.4)
Black/African American		12 (14.0)	24 (14.0)
White		50 (58.1)	111 (64.5)
Weight, mean (SD), kg		78.9 (23.6)	75.4 (22.7)
BMI, mean (SD)		28.3 (7.3)	27.1 (6.8)
Geographic region			
United States		63 (73.3)	122 (71.0)
Europe		14 (16.3)	33 (19.2)
Rest of the world		9 (10.5)	17 (9.9)
Prior systemic treatment			
Systemic corticosteroids		30 (34.9)	57 (33.1)
Phototherapy		19 (22.1)	31 (18.0)
Dupilumab		12 (14.0)	28 (16.3)
Cyclosporine		6 (7.0)	22 (12.8)
Methotrexate		8 (9.3)	16 (9.3)
Janus kinase inhibitors		6 (7.0)	7 (4.1)
Photochemotherapy (PUVA)		3 (3.5)	4 (2.3)
Mycophenolate-mofetil		0	5 (2.9)
Tralokinumab		2 (2.3)	3 (1.7)
Other biologics		7 (8.1)	20 (11.6)
A mean (SD) of the number of years since AD diagnosis		20.7 (14.3)	20.3 (16.1)

Frequently recurrent and chronic skin disorders, atopic dermatitis (AD) can adversely affect quality of life for patients suffering from it. A majority of AD cases occur in children, with 20 percent of all

children around the world infected. Two percent to seven percent of AD cases occur in adults. A significant part of the disease is excessive itching, sleeping disturbances, and skin pain, which are disruptive to daily life and social interaction. It is important to note that AD is a disease burdened disease, and severe cases of such symptoms may cause a great deal of emotional and psychological distress. Depending on the severity of AD, treatment differs. The mild cases of this condition have been treated extensively with topical corticosteroids (TCS) and emollients. In cases of moderate-to-severe AD, however, other systemic therapies or phototherapy may be necessary. Through the years, some target biologic therapy was invented, including dupilumab and tralokinumab, also known as Janus kinase inhibitors. Using these interventions, good results are guaranteed in the treatment of moderate-severe AD, because they attack single components of the immune system that trigger inflammation. In spite of these improvements, new therapeutic opportunities are needed, since AD is heterogeneous, and not all patients would respond to a given treatment. The proinflammatory cytokine interleukin-13 (IL-13) is one of the potential targets of therapy for AD and plays a critical role in the pathogenesis of inflammation. It has shown great clinical benefit in both phase 2b and phase 3 trials of Lebrikizumab, a monoclonal antibody that blocks exclusively IL-13. In these studies, lebrikizumab was shown to be significantly useful in redesigning the outcomes of moderate-to-severe Alzheimer's disease patients. The use of biologics as a monotherapy on a regular basis is not recommended, and it would be more effective to use them with TCS, which appears to be commonly used in the treatment of AD. An effectiveness and safety comparison study was conducted with low- to mid-potency TCS along with lebrikizumab, both of which were used to treat moderate-to-severe Alzheimer's. It was concluded from the trial that the combination of lebrikizumab and TCS therapy improved disease outcomes, which is relevant data regarding the long-term use of biologics in conjunction with topical treatment for AD.

Discussion

As the first randomized and placebo-controlled trial, the Dhere clinical trial is underway; this is a placebo controlled and double blind trial determining whether lebrikizumab should be used in combination with topical corticosteroids to treat moderate-severe atopic dermatitis (AD) in adults and adolescents. As part of this research, topical therapies such as lebrikizumab are given as an as-needed intervention, and systemic agents such as lebrikizumab are taken as a systemic agent. At the 16th week of treatment, all primary and key endpoints had been met. As compared to a placebo group, the lebrikizumab plus TCS group demonstrated a considerable improvement in the EASI -75 reaction and the IGA (0,1) reaction at week 4. Even in week four, the severity of the disorder itself, which has a significant impact on a patient's quality of life, was positively modified. In accordance with the international consensus, composite endpoints should be used to measure the effectiveness of treatments on a global scale. Patients in the LEB+TCS group were more than twice as likely to achieve the composite endpoint than those in the ADhere trial, which measured physician-rated skin clearance (EASI-75) and patient-rated changes in itch (Prirititus NRS). There may be a close match between this combination of TCS therapy and the clinical procedures used in treating AD, where TCS may be utilized conditional to the patient's requirements. There was a statistically significant increase in TCS/TCI free days in LEB+TCS compared with placebo, although there was some purpose in capturing TCS/TCI data in order to conduct the analysis. Although the combined treatment also had the same response rates as monotherapy literature, some end points of response were improved. According to ADhere, EASI-75 was extracted in 70 percent of patients with LEB + TCS, but 59 and 52 respectively in ADvocate 1 and 2. Based on previous research studies, the adverse effects reported by LEB+TCS are mild or moderate as compared to those reported by other research studies. In addition to conjunctivitis and headaches, other IL-13 and IL-4 biologics caused most side effects. Lebrikizumab monotherapy caused a higher rate of conjunctivitis, but it was lower than in the LEB +TCS study. Since the withdrawal rate of the treatment (2.1) is relatively low following adverse events, time can also be considered a safe factor in combination therapy. Additionally, no deaths have been reported, making the combination therapy safe. In addition, since the trial will involve a heterogeneous sample

of patients, including adolescents and people of other races, it is more likely that the trial will become part of clinical practice. A continuous clinical development program for lebrikizumab consists of two monotherapy trials, ADhere and ADjoin, which are both undergoing long-term extension trials and phase 3 trials to determine the effect of lebrikizumab on adult vaccine immune responses. Thus, this research may prove useful in learning about the clinical benefits of biologics that are used alongside topical procedures to treat moderate-to-severe AD by evaluating lebrikizumab as an adjunct to TCS.

Conclusion

Based on the ADhere phase 3 clinical trial, it can be concluded that lebrikizumab is effective in the treatment of moderate to severe atopic dermatitis in adults as well as children when combined with low- to mid-potency topical corticosteroids (TCS). According to the research, major changes in disease outcomes, such as clearer skin, less itchiness, and disruption of sleep, were experienced as early as week four. In the real world, the use of topical therapies in conjunction with systemic therapies is frequently prevalent, which means that such a treatment mix is rather compatible with current clinical practices. In comparison to previous studies, lebrikizumab showed similar safety profiles, with mild to moderate adverse effects most commonly reported. According to the ADhere study outcomes, combining biologics with topical therapy may be a beneficial approach to treating AD over the long term. As a result of this study, a broader scope of therapeutic interventions for moderate-severe AD patients will be developed, and further research will be developed in this field.

References

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet*. 2020;396(10247):345–360.
2. Harrop J, Chinn S, Verlato G, et al. Eczema, atopy and allergen exposure in adults: a population-based study. *Clin Exp Allergy*. 2007;37(4):526–535.
3. Diepgen TL, Ofenloch RF, Bruze M, et al. Prevalence of contact allergy in the general population in different European regions. *Br J Dermatol*. 2016;174(2):319–329.
4. Sacotte R, Silverberg JI. Epidemiology of adult atopic dermatitis. *Clin Dermatol*. 2018;36(5):595–605.
5. Saeki H, Tsunemi Y, Fujita H, et al. Prevalence of atopic dermatitis determined by clinical examination in Japanese adults. *J Dermatol*. 2006;33(11):817–819.
6. Yosipovitch G, Papoiu AD. What causes itch in atopic dermatitis? *Curr Allergy Asthma Rep*. 2008;8(4):306–311.
7. Silverberg JI, Gelfand JM, Margolis DJ, et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. *Ann Allergy Asthma Immunol*. 2018;121(3):340–347.
8. Vakharia PP, Chopra R, Sacotte R, et al. Burden of skin pain in atopic dermatitis. *Ann Allergy Asthma Immunol*. 2017;119(6):548–552.e3.
9. Ricci G, Bellini F, Dondi A, Patrizi A, Pession A. Atopic dermatitis in adolescence. *Dermatol Reports*. 2011;4(1):e1.
10. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338–351.
11. Sidbury R, Davis DM, Cohen DE, et al.; American Academy of Dermatology. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71(2):327–349.
12. Thibodeaux Q, Smith MP, Ly K, Beck K, Liao W, Bhutani T. A review of dupilumab in the treatment of atopic diseases. *Hum Vaccin Immunother*. 2019;15(9):2129–2139.
13. Stölzl D, Weidinger S, Drerup K. A new era has begun: Treatment of atopic dermatitis with biologics. *Allergol Select*. 2021;5:265–273.

14. Drucker AM, Morra DE, Prieto-Merino D, et al. Systemic immunomodulatory treatments for atopic dermatitis: update of a living systematic review and network meta-analysis. *2022;158(5):523–532.*
15. Wollenberg A, Barbarot S, Bieber T, et al.; European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), the European Academy of Allergy and Clinical Immunology (EAACI), the European Task Force on Atopic Dermatitis (ETFAD), European Federation of Allergy and Airways Diseases Patients' Associations (EFA), the European Society for Dermatology and Psychiatry (ESDaP), the European Society of Pediatric Dermatology (ESPD), Global Allergy and Asthma European Network (GA2LEN) and the European Union of Medical Specialists (UEMS). Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol*. 2018;32(5):657–682.
16. Wollenberg A, Barbarot S, Bieber T, et al.; European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), the European Academy of Allergy and Clinical Immunology (EAACI), the European Task Force on Atopic Dermatitis (ETFAD), European Federation of Allergy and Airways Diseases Patients' Associations (EFA), the European Society for Dermatology and Psychiatry (ESDaP), the European Society of Pediatric Dermatology (ESPD), Global Allergy and Asthma European Network (GA2LEN) and the European Union of Medical Specialists (UEMS). Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol*. 2018;32(6):850–878.
17. Bieber T. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. *Allergy*. 2020;75(1):54–62.
18. Moyle M, Cevikbas F, Harden JL, Guttman-Yassky E. Understanding the immune landscape in atopic dermatitis: The era of biologics and emerging therapeutic approaches. *Exp Dermatol*. 2019;28(7):756–768.
19. Tsoi LC, Rodriguez E, Degenhardt F, et al. Atopic dermatitis is an IL-13-dominant disease with greater molecular heterogeneity compared to psoriasis. *J Invest Dermatol*. 2019;139(7):1480–1489.
20. Okragly A, Ryuzoji A, Daniels M, Patel C, Benschop R. Comparison of the affinity and in vitro activity of lebrikizumab, tralokinumab, and cendakimab. Paper presented at: *Inflammatory Skin Disease Summit*. November 06, 2021; New York, New York.
21. Guttman-Yassky E, Blauvelt A, Eichenfield LF, et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. *JAMA Dermatol*. 2020;156(4):411–420.
22. Silverberg JI, Thaçi D, Seneschal J, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: results from two phase 3, randomized, double-blinded, placebo-controlled trials. Paper presented at: *American Academy of Dermatology*; 2022; Boston, MA.
23. Pillai S, Thaci D, Guttman-Yassky E, Simpson E, Blauvelt A, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: results from two phase 3, randomized, double-blinded, placebo-controlled trials. *American Academy of Dermatology – 80th Annual Meeting*. March 26, 2022; Boston, Massachusetts.
24. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol*. 2019;143(1):1–11.
25. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191–2194.
26. Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*. 2015;74(12):2107–2116.

27. De Bruin-Weller M, Biedermann T, Bissonnette R, et al. Treat-to-target in atopic dermatitis: an international consensus on a set of core decision points for systemic therapies. *Acta Derm Venereol*. 2021;101(2):adv00402.
28. Simpson EL, Flohr C, Eichenfield LF, et al. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: a randomized, placebo-controlled phase II trial (TREBLE). *J Am Acad Dermatol*. 2018;78(5):863–871.e11.
29. ClinicalTrials.gov. A study to evaluate the safety of lebrikizumab compared to topical corticosteroids in adult patients with atopic dermatitis. Accessed May 6, 2022.
30. Hansen PM, Tollenaere MAX, Hedengran A, et al. IL-4 and IL-13 both contribute to the homeostasis of human conjunctival goblet cells in vitro. *Allergy*. 2022;77(8):2555–2558.
31. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomized, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287–2303.
32. Gutermuth J, Pink AE, Worm M, Soldbro L, Bjerregård Øland C, Weidinger S. Tralokinumab plus topical corticosteroids in adults with severe atopic dermatitis and inadequate response to or intolerance of ciclosporin A: a placebo-controlled, randomized, phase III clinical trial (ECZTRA 7). *Br J Dermatol*. 2022;186(3):440–452.