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REVIEW

Managing Atopic Dermatitis with Lebrikizumab – The Evidence to Date

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Abstract: Atopic dermatitis is a prevalent, inflammatory skin disease that presents with an eczematous, itchy rash. As of late, there have been many emerging monoclonal antibody inhibitor and small molecule therapies that have changed the course of eczema treatment. One of the treatments in the pipeline for atopic dermatitis is interleukin 13 monoclonal antibody inhibitor, lebrikizumab. As interleukin 13 has been identified as a pro-inflammatory cytokine in the immunological cascade of eczema, it is thought that lebrikizumab can be a great treatment choice for patients with atopic dermatitis. Lebrikizumab is currently being investigated in several studies. Thus far, lebrikizumab for the treatment of eczema has been found to be efficacious; in particular, a rapid response of pruritus improvement has been demonstrated in as early as 2 days. Additionally, it is well tolerated and has an acceptable safety profile, with reports suggesting that are decreased risks of infection when compared to dupilumab. In this review, we aim to summarize the current understanding of lebrikizumab in terms of the mechanism of action, preclinical pharmacology, pharmacokinetics and metabolism, efficacy and safety, and drug indications.

Keywords: lebrikizumab, IL-13, monoclonal antibody inhibitor, atopic dermatitis, eczema

Background

Atopic dermatitis (AD) is an inflammatory skin condition that affects many individuals. It is approximated that 15–20% of children and 3% of adults are diagnosed with the skin disease; the global prevalence rate has been stable between 1990 and 2017, although the prevalence peaks in childhood and older populations and varies in geographic distribution.[1,2] Some reports have found that AD is increasing 2-to-3 fold. As the prevalence of AD is significant and the incidence is increasing, AD has large implications to affected individuals and the health-care system. AD has been found to profoundly impact quality of life.[3–5] Considering this, there is significant need for more efficacious treatments.

Eczema is a complex skin condition that results in inflammatory skin changes with many phenotypes that persist for a long period of time. Although the presentation of AD can vary, the most common is acute flares of dermatitis appearing among a background of dry skin. The dermatitis is classically described as scaly, erythematous, edematous, vesicular, and lichenified, affecting flexor regions of the arms and legs, as well as the face and trunk. In addition to skin lesions, affected areas are also intensely pruritic, with 80–100% of patients reporting itch.[6]

Although the pathogenesis of AD is not entirely understood, it is known that there is an interplay between skin barrier dysfunction, an aberrant T helper cell type 2 (Th2)-mediated immune response, and neural sensitization. These underlying mechanisms co-interact to produce a vicious itch-scratch cycle that continues to exacerbate the dermatitis and pruritus of AD. With this knowledge in mind, the treatments of AD work to diminish these molecular changes. In the last decades, the treatment of AD had remained largely unchanged. Mainstay treatments consisted of topical corticosteroids and calcineurin inhibitors as well as frequent emollient application.[7,8] In more severe cases, systemic corticosteroids were employed to curb flares. However, these treatments were not suitable long-term therapies due to various adverse effects and their broad mechanism of action did not specifically address key players in the AD immunological cascade. Additionally, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil are immunotherapies that have

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been traditionally used; although, they are less appealing choices due to broad targets and side effects.[9] Therefore, there is a necessity for more AD-specific treatments.

As of late, monoclonal antibody inhibitors and small molecule treatments have been introduced to the market and have demonstrated great therapeutic efficacy with a more favorable side-effect profile. These include interleukin (IL) 4 and IL-13 inhibitor, dupilumab, IL-13 inhibitor tralokinumab, and janus-kinase (JAK) inhibitors, abrocitinib, baricitinib, and upadacitinib. In addition to these treatments, there are other biologic therapies that are currently being investigated for the treatment of AD. Lebrikizumab, an IL-13 antagonist, is one of these treatments. Lebrikizumab is a subcutaneous drug that functions as an IL-13 inhibitor; it neutralizes the cytokine and prevents binding and heterodimerization of IL-13Rα1 and IL-4Rα.[10] IL-13 has demonstrated a significant role in the pathobiology of AD, the inhibition of this inflammatory cytokine has a promising outlook on the ability to decrease disease-related findings of AD. Tralokinumab, as mentioned above, is another IL-13 inhibitor; yet, the two monoclonal antibody inhibitors have distinct epitopes to IL −13, which effects their role in IL-13 antagonism.[11] While lebrikizumab neutralizes IL-13 activity on IL-13Rα1 and IL-4Rα, tralokinumab prevents IL-13 interaction with IL-13Rα1 and IL-13Rα2, eliciting a degree of dissimilarity.[11] Dupilumab also inhibits IL-13 by antagonizing the IL-4Rα receptor, which is shared by IL-4 and IL-13.

An overlook of the pathophysiology AD reveals that genetics, epidermal dysfunction, immune dysregulation, and neural changes can all be associated with IL-13.[12,13] One study on RNA pathways demonstrated that IL-13 was one of the dominant cytokines exhibited in AD.[14] The most apparent genetic difference observed in AD patients is irregular filaggrin (FLG).[12,15,16] FLG is a major structural protein found in the stratum corneum. FLG loss-of-function mutations have been widely associated with AD development, causing decreased expression of the protein, and contributing to weakened skin defenses. Besides FLG, it has also been found that there is an association between immune genetic polymorphisms and the development of AD. Namely, alterations in Th2 immune response yields increased production of IL-4 and IL-13, which in return decrease the expression of FLG.[13,17] IL-13, among other pro-inflammatory cytokines, has also been found to downregulate other skin defense components, such as keratins, loricrin, involucrin, and cell adhesion molecules.[13,17] Additionally, there is also an upregulation of IL-4 and IL-13 via gain of function polymorphism of the Th2 cellular lines.[13] These changes work to ultimately create a background of skin barrier dysfunction that propagates AD via increased trans-epidermal water loss, increased exposure to allergens, and upregulated immune responses.

Besides the role that cytokines IL-4 and IL-13 play in the skin barrier dysfunction, these upregulated molecules in the pathophysiology of AD promote an amplified Th2 immune response in the acute phase of AD.[18] These changes include increased chemokine production, decreased antimicrobial peptides, and intensified allergic inflammation.[13] IL-13 is produced by Th2 cells, mast cells, basophils, eosinophils, innate type 2 cells, natural killer T cells, and macrophages.[19] It binds to receptor IL-13Rα1/IL-4Rα to activate downstream signal transducer and activator of phosphorylation (STAT) to increase cytokine and chemokine production and provoke itch.[13,19] Another role that IL-13 plays in the mechanism of AD is neuroimmune sensitization. IL-13 has been found to activate nerves via the IL-13 associated receptors and JAK receptors, increasing the symptom of itch via non-histaminergic pathways.[13] A recent study demonstrated that IL-13 plays a direct enhancer in neural itch pathways in human dorsal root ganglion.[20] Ultimately, IL-13 plays an integral role to the development of AD and the antagonism of IL-13 can attenuate the disease.

Preclinical Pharmacology

Much of the preclinical data on lebrikizumab can be extrapolated from studies on asthma models. In a 2004 study, Yang et al created a chronic asthma model by exposing mice to repeated intranasal antigens.[21] A group of mice was administered anti-IL-13 monoclonal antibodies with each allergen exposure. The treated mice demonstrated decreased pro-inflammatory markers, such as decreased eosinophilic infiltration of up to 50%, decreased Th2 cytokines IL-4 and IL-5, decreased inflammatory cytokines IL-6 and tumor necrosis factor alpha (TNFα), and decreased chemokines.[21] One study evaluated the use of IL-13 monoclonal antibodies in murine models.[22] Two antibodies were generated, with slightly distinct mechanisms of action in terms of IL-13 inhibition. One antibody was shown to bind to mouse IL-13 and prevent its binding to mIL-13Rα1; the other antibody similarly targeted IL-13 but instead prevented the assembly of IL-4Rα with the IL-13/IL-13Rα1 complex. The antibodies were independently administered to mice that were stimulated with mouse IL-13. The results revealed that STAT-6 activation was downregulated by both IL-13 antibody subtypes.[22]

Similarly, another study evaluated two antibodies in atopic-disease models: one inhibiting IL-13 binding to IL-4Rα and one inhibiting IL-13 binding to IL-13Rα1.[23] Cynomolgus monkeys were sensitized with Ascaris suum antigen, and the level of immunoglobulin E was evaluated in treatment and control groups. The study found that the administration of either antibody resulted in increased IL-13 levels yet no associated biological activity, indicating successful blockade and inhibition of IL-13 downstream effects.[23] Martin et al conducted a study that evaluated the role of an anti-IL-13 monoclonal antibody in macaques with or without allergic asthma.[24] The administration of IL-13 in the uninhibited macaques demonstrated a dose-dependent increase in STAT-6 phosphorylation; when IL-13 was administered to anti-IL-13 monoclonal antibody-treated macaques, there was an observed inhibition of IL-13.[24]

Although this data is not a direct representation of IL-13 inhibition in AD, the shared Th2-mediated immune responses between AD and asthma can provide insight on the role of anti-IL-13 treatment in AD. Miron et al recently demonstrated that lebrikizumab has a significant anti-pruritic effect by inhibiting human dorsal root ganglion cells.[20]

Pharmacokinetics and Metabolism

Studies on the pharmacokinetics of lebrikizumab have found linear, dose-proportional characteristics. Initial studies for lebrikizumab for adult asthma have yielded important information on the pharmacokinetics of lebrikizumab that have helped guide clinical trials in AD patients. Noonan et al measured serum lebrikizumab levels at several time points throughout monthly drug administration and 12 weeks after the last dose of treatment in asthmatic patients and found that steady-state conditions were reached before 12 weeks and observed concentrations were dose-proportional. Mean terminal elimination half-life was 25 days.[25] Similarly, several other trials for the treatment of asthma also found linear dose-proportional pharmacokinetic profiles of the drug.[19,26]

The results of studies on the pharmacokinetics of lebrikizumab in AD patients are reflective of those found in clinical trials for adult asthma. In a Phase II clinical trial conducted by Simpson et al (TREBLE), lebrikizumab was given to 3 different experimental groups of AD patients by either a single dose of 125 mg, a single dose of 250 mg, or 125 mg doses every 4 weeks. A higher single dose of 250 mg lebrikizumab yielded the highest maximum lebrikizumab concentration in the first week, and all single doses gradually tapered down in mean minimum lebrikizumab concentration over the course of 12 weeks. Meanwhile, patients receiving 125 mg every 4 weeks were found to have a gradually increasing minimum lebrikizumab concentration over the course of 12 weeks. The half-life of lebrikizumab was found to range from 18.5 to 22.2 days across all groups.[27] The linear pharmacokinetic profile and relatively long half-life of the drug allows for the relatively sparse dosing of lebrikizumab every 4 weeks and suggests that there may be even less of a need for frequent dosing during maintenance.

The metabolic pathway of lebrikizumab is not well studied, but as a IgG_4 humanized monoclonal antibody, it is presumed to be metabolized by proteolytic degradation similarly to endogenous IgG. A single joint mutation on the hinge portion of the molecule increases lebrikizumab's stability.[28]

Clinical Efficacy and Safety

To date, there are 2 phase II clinical trials that have evaluated the efficacy and safety of lebrikizumab in patients with moderate-to-severe AD (Table 1); although, there are numerous other clinical trials that are currently underway to continue investigating lebrikizumab. In 2018, Simpson et al conducted a randomized, placebo-controlled, double-blind, phase II study in a total of 209 patients aged 18 years or older with moderate-to-severe AD.[27] Patients were randomized to receive a single dose of 125 mg of lebrikizumab, a single dose of 250 mg of lebrikizumab, a lebrikizumab dose of 125 mg every 4 weeks, or placebo for a total of 12 weeks. In addition to lebrikizumab therapy, patients were also required to use topical corticosteroids twice a day. The study primarily evaluated for patients who achieved Eczema Area and Severity Index (EASI)-50 at the end of the study period. At the end of the study, patients who received 125 mg of lebrikizumab every 4 weeks demonstrated a significant improvement in EASI-50 when compared to placebo, specifically 82.4% treatment patients compared to 62.3% control patients ($p = 0.026$).[27] Both the 125 mg and 250 mg single-dose treatment groups did not demonstrate significant improvements in EASI-50 compared to placebo.[27]

In terms of secondary study outcomes, EASI-75 and Scoring Atopic Dermatitis (SCORAD)-50 occurred in 54.9% and 51.0% of patients treated with 125 mg of lebrikizumab every 4 weeks when compared to the placebo group, respectively

Table 1 Summary of Randomized Controlled Trials Evaluating Lebrikizumab in Patients with AD

Study	Medication	Condition	Design	Patients	Study Endpoints	Efficacy	Adverse Effects
Simpson et al 2018[27]	Lebrikizumab	AD	• Randomized, placebo-controlled, double-blind, phase II study • 12 weeks	N= 209	• Efficacy (EASI-50, EASI-75, SCORAD-50, IGA BSA, pruritus VAS) • Quality of life (sleep loss VAS, ADIQ, DLQI) • Safety and tolerability	• 82.4% of patients who received 125 mg of lebrikizumab every 4 weeks compared to 62.3% of control patients (p= 0.026) demonstrated EASI-50 • EASI-75 and SCORAD-50 occurred in 54.9% and 51.0% of patients treated with 125 mg of lebrikizumab every 4 weeks when compared to the placebo group, respectively (p=0.036; p=0.012)	• Well tolerated • Adverse effects were mild and transient • There was no significant difference between adverse effects, serious adverse effects, events leading to drug discontinuation, and risk of infection between treatment and control • No reports of death, anaphylaxis, or malignancies
Guttman-Yassky et al 2020[29]	Lebrikizumab	AD	• Double-blind, placebo-controlled, dose-ranging randomized phase II clinical trial • 16 weeks	N= 280	• Efficacy (EASI, IGA, BSA, and pruritus NRS) • Safety and tolerability	• Dose dependent improvement in EASI of −62.3% for 125 mg every 4 weeks (37.3%, p = 0.02), −69.2% for 250 mg every 4 weeks (38.3%, p = 0.002), and −72.1% for 250 mg every 2 weeks (37.2%, p < 0.001) patient groups when compared to −41.1% (56.5%) in the placebo • EASI-50, EASI-75, EASI-90, IGA scores of 0/1, and BSA improvements were statistically significant in both lebrikizumab 250 mg treatment groups • 70.0% of patients in the lebrikizumab 250 mg Q2W group, compared to 7.3% of placebo patients (p < 0.001), demonstrated a 4 point or greater reduction in pruritus NRS	• Well-tolerated • Consistent safety to previous trials • Most common adverse effects were upper respiratory tract infections (7.5% in all treatment groups; 5.8% in control), nasopharyngitis (6.6% in all treatment groups; 3.8% in control), headache (3.5% in all treatment groups, 5.8% in control), injection site pain (3.1% in all treatment groups; 1.9% in control), and fatigue (1.8% in all treatment groups; 0% in control) • Injection site reactions (5.7% in all treatment groups; 1.9% in control) • Herpes-related infection (3.5% in all treatment groups; 3.8% in control) • Conjunctivitis (2.6% in all treatment groups, 0% in control)

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; SCORAD, Scoring Atopic Dermatitis; IGA, Investigator's Global Assessment; BSA, body surface area; VAS, visual analogue score; ADIQ, Atopic Dermatitis Impact Questionnaire; DLQI, Dermatology Life Quality Index; NRS, numerical rating score.

(p = 0.036; p = 0.012); EASI-75 findings were not statistically significant in either single dose treatment groups, but SCORAD-50 occurred in 47.2% of patients in the 250 mg single dose group (p = 0.030).[27] Additionally, Investigator's Global Assessment (IGA) scores were all improved in lebrikizumab groups.[27] Body surface area (BSA) was also most improved in the continually treated group; although, the findings were not statistically significant.[27] Lastly, pruritus visual analogue scores (VAS) were reduced in all groups (34.9%, 32.8%, 40.7%, and 27.5% in the lebrikizumab 125 mg single dose, 250 mg single dose, 125 mg every 4 weeks groups, and placebo group, respectively[27]). It appears that all groups demonstrated some improvement in pruritus due to the study protocol requiring twice-daily topical corticosteroid administration. Relative to placebo, there were also improvements in sleep loss VAS, Atopic Dermatitis Impact Questionnaire (ADIQ), and Dermatology Life Quality Index (DLQI) in treatment groups.[27] Limitations of this study include the background use of topical corticosteroids, which made it difficult to assess certain outcomes in the treatment groups when compared to placebo, however it better reflects real-world outcomes of use of this drug.

Of importance, this study demonstrates that lebrikizumab provides therapeutic benefit to patients already on an aggressive topical regimen.[27] Additionally, the data suggests that 12 weeks may not be enough time to reach response plateau as trends were still peaking.[27] Results may be dose dependent as determined by the study protocol.[27] The blockade of IL-4 and IL-13 has been demonstrated efficacy via dupilumab; however, the use of lebrikizumab may also provide efficacy via a narrower target.[27]

Regarding safety, lebrikizumab was found to be well tolerated and adverse effects were mild and transient, lasting a median of 1–3 days.[27] Between treatment and placebo groups, there was no significant difference between adverse effects, serious adverse effects, events leading to drug discontinuation, and risk of infection.[27] Seventy percent of patients in the lebrikizumab 125 mg single dose group, 75% of patients in the lebrikizumab 250 mg single dose group, 54% of patients in the lebrikizumab 125 mg Q4W, and 66% of patient in the placebo group reported at least one adverse effect.[27] Of interest, there were adverse effects related to infections (44%, 39%, 24%, and 45%), consisting of skin infections (11%, 10%, 6%, and 17%), herpes infection (2%, 6%, 4%, and 0%), and conjunctival infections (13%, 10%, 6%, and 8%) in the lebrikizumab 125 mg single dose, 250 mg single dose, 125 mg every 4 weeks groups, and placebo group, respectively.[27] Additionally, 2 patients in the lebrikizumab 125 mg Q4W group and 1 patient in the placebo group experienced injection site reactions.[27] There were no reports of serious drug effects: death, anaphylaxis, or malignancies.[27]

Guttman-Yassky et al performed a double-blind, placebo-controlled, dose-ranging randomized phase II clinical trial on the use of lebrikizumab in moderate-to-severe AD.[29] Two hundred and eighty patients were randomized (2:3:3:3) as follows: placebo every 2 weeks, 125 mg of lebrikizumab Q4W after a 250 mg loading dose, 250 mg of lebrikizumab Q4W after a 500 mg loading dose, or 250 mg of lebrikizumab Q2W after a 500 mg loading dose and an additional loading dose at week 2. The study spanned over 16 weeks. EASI, IGA, and pruritus numerical rating scores (NRS) were assessed.

The study found a dose-dependent improvement in EASI of −62.3% for 125 mg every 4 weeks (37.3%, p = 0.02), −69.2% for 250 mg every 4 weeks (38.3%, p = 0.002), and −72.1% for 250 mg every 2 weeks (37.2%, p < 0.001) patient groups when compared to −41.1% (56.5%) in the placebo group.[29] Additionally, EASI-50, EASI-75, EASI-90, IGA scores of 0/1, and BSA improvements were statistically significant in both lebrikizumab 250 mg treatment groups.[29] Improvement in least squares mean percentage change for pruritus NRS was statistically significant in a dose-dependent fashion for all treatment groups.[29] Additionally, more patients in the lebrikizumab treatment arms experienced meaningful reductions of pruritus NRS by 4 points or greater: 70.0% of patients in the lebrikizumab 250 mg Q2W group, compared to 7.3% of placebo patients (p < 0.001).[29] 15.3% of these patients experienced 4 points or greater of pruritus NRS in as early as 2 days, when compared to 4.5% of placebo patients.[29] In the lebrikizumab 125 mg Q4W and 250 mg Q4W, 6.3% and 5.6% also demonstrated a 4 point or greater reduction of pruritus NRS in 2 days, respectively.[29] Interestingly, 16 patients enrolled in the study self-reported prior treatment with dupilumab, 4 in the placebo arm and 12 in the treatment arms. At 16 weeks, 5/12 achieved EASI-75 and 4/12 achieved IGA scores of 0/1, compared to 0/4 placebo patients.[29] Considering the overlap in treatment targets, these results may further support the use of lebrikizumab to antagonize cytokine IL-13 more directly in the immunological cascade of AD. The targeting of IL-13 alone may be sufficient in providing therapeutic efficacy.

The prevalence of at least one adverse effect did not differ greatly between placebo (24; 46.2%) and treatment groups (42 [57.5%], 39 [48.8], and 46 [61.3] in the lebrikizumab 125 mg Q4W, 250 Q4W, and 250 Q2W groups, respectively).[29] 3.8% of patients in the placebo group, compared to 2.7%, 0%, and 2.7% of the respective treatment groups, experienced one or more serious adverse effects. None of the serious adverse effects were thought to be related to treatment.[29] There were no deaths reported in the study. The most common adverse effects were upper respiratory tract infections (7.5% in all treatment groups; 5.8% in control), nasopharyngitis (6.6% in all treatment groups; 3.8% in control), headache (3.5% in all treatment groups, 5.8% in control), injection site pain (3.1% in all treatment groups; 1.9% in control), and fatigue (1.8% in all treatment groups; 0% in control).[29] Of interest, injection site reactions (5.7% in all treatment groups; 1.9% in control), herpes-related infection (3.5% in all treatment groups; 3.8% in control), and conjunctivitis (2.6% in all treatment groups, 0% in control) occurred at low rates in the treatment groups.[29] This data suggests that the occurrence of conjunctivitis, a prominent side effect of dupilumab (9–38%), is lower with lebrikizumab.[29] Overall, lebrikizumab is well tolerated and demonstrated consistent safety to previous trials.

Currently, there is one phase II clinical trial (NCT02465606), and 8 Phase III clinical trials (NCT04250350, NCT04392154, NCT04178967, NCT04146363, NCT04250337, NCT05149313, NCT04760314, NCT04626297) that are assessing the treatment of lebrikizumab in moderate-to-severe AD.

Indication and Drug Interactions

Lebrikizumab is currently undergoing phase III clinical trials for approval in use in atopic dermatitis and has been granted Fast Track designation by the FDA for moderate-to-severe atopic dermatitis in adults and adolescents. Preliminary results of these phase III trials suggest that it may significantly improve disease severity when combined with topical steroids.[30] Besides atopic dermatitis, clinical trials have also been conducted for treatment in IL-13 associated conditions such as asthma, idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease.[19,25–27,31–33]

Currently, there are limited data on the drug-to-drug interactions of lebrikizumab. This is an area that needs further evaluation to determine whether patients on other pharmacological therapies can safely and effectively take lebrikizumab.

Conclusion

AD is a prevalent, chronic inflammatory skin condition; the introduction of novel treatments has better targeted the key molecular players involved in AD pathogenesis and provided enhanced therapeutic efficacy as well as quality of life. One of the emerging treatments for AD is IL-13 cytokine inhibitor, lebrikizumab. Lebrikizumab has been evaluated to tackle the inflammatory process underlying AD. As IL-13 has been found to play a role in skin barrier dysfunction, immune dysregulation, pruritus, and neural sensitization, the inhibitory effect of lebrikizumab is thought to mitigate the disease course.

Thus far, the available data suggests that the inhibition of IL-13 is efficacious at diminishing lesions and rapidly decrease pruritus. In these early clinical trials, the efficacy of lebrikizumab is loosely compared to dupilumab, which also antagonizes IL-13 by inhibiting IL-4Rα, a shared receptor for both IL-4 and IL-13. These preliminary evaluations have found that the sole inhibition of IL-13 can also be sufficient at alleviating disease-related findings of AD; additionally, the use of lebrikizumab was found to be effective in some patients that failed dupilumab. Lebrikizumab has a good safety profile, as it is overall well tolerated. Adverse effects are typically mild and transient in nature, requiring none or simple supportive measures. Side effects such as skin infection, herpes-related infection, and conjunctivitis occur at rates similar to dupilumab, and one study reported that the prevalence of conjunctivitis was lower in lebrikizumab when compared to real-world data from dupilumab. Both IL-13 inhibitors differ in their binding epitopes and their ability to block one or both receptors of IL-13; currently, it is unknown whether these differences have clinical importance. This is due to differences in the study design, including permitted corticosteroid use during studies and differing doses of each drug. As a result, it is difficult to compare efficacy between the agents and establish direct comparisons from the findings.

Therefore, these findings suggest that lebrikizumab can meaningfully impact the future of AD treatment by providing an alternative, effective, and safe choice among other treatments via its more direct mechanism of action against pro-inflammatory cytokine IL-13.

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