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EFFICACY OF TRALOKINUMAB MONO THERAPY IN ADOLESCENTS WITH SEVERE ATOPIC DERMATITIS

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ABSTRACT

Adolescents with moderate or severe forms of atopic dermatitis (AD) have limited treatment options. It is intended to determine whether TRALOKINIUMAB monotherapy can reduce AD symptoms in adolescents with interleukin-13-responsive AD and is safe, along with its efficacy. The investigator's global assessment was completed by 24 to 34 patients with severe and moderate AD (IGA score 3; EASI 16). Randomization was made between patients (1:1:1) and tralokinumab (75 or 150 mg). Without maintenance treatment after week 16 without rescue medication, those with 0 or 1 IGA score and/or EASI 75 score improved 75% to 100%; others A 2-week cycle of 150 mg of tralokinumab was switched to open-label tralokinumab. Obtaining either an IGA score of 0 or 1 or an EASI score of 75 was the primary endpoint at week 16 The median age of the 144 patients randomized was 14 with 74 males. The proportion of patients who achieved an IGA score of 1 or 0 without rescue medication at week 16 following 75 mg tralokinumab (n = 47; 2) and 150 mg tralokinumab (n = 49) was higher than that of placebo (n = 48). The adjusted difference was 16.4% (95% CI, 8.4%-24.6%); P <0.002, and the difference was 12.7% (95 % CI, 5.3%-22.3%); P <0.002). There was no difference between treated patients and placebo at week 16 (adjusted difference, 21.4% [95% CI, 11.3%-31.5%]; P<0.001) due to tralokinumab 75mg and 150 mg without rescue. Compared to placebo, tralokinumab 75 mg or 150 mg improved four or more points on the Adolescent Worst Pruritus Numeric Rating Scale. There was a decrease of 27.5% in Scoring AD (and a decrease of 28% in Scoring AD) with tralokinumab, 75 mg, and 150 mg when compared to placebo (-4.1%). There was a decrease in Children's Dermatology Life Quality Index by 9.5% and a decrease in Scoring AD by 5% when compared to placebo. In every case where the primary end point was met at week 16, no tralokinumab was required for rescue. 32.2 percent of participants achieved an IGA score of 0 or 1, whereas 56.7% achieved an EASI score of 75. Week 52 did not see a conjunctivitis outbreak. Talokinumab side effects were mild.

Key words: Tralokinumab, Children, Dermatology Life.

INTRODUCTION

As well as microbiome dysbiotics, adolescents with AD can suffer from psychological issues, difficulties at school, and disruption of their skin barrier [1]. Tralokinumab is an IgG antibody targeting the IL-13 signaling pathway in humans.18 However, by blocking the IL-4R, duplilumab inhibits IL-4 and IL-13 signaling, also approved for the treatment of AD in adolescents [2-6]. In this article, we present data from ECZTRA 6, a phase 3, double-blind, randomized, double-blind, placebo-controlled study comparing tralokinumab monotherapy with placebo for adolescents with moderate to severe AD.

TECHNIQUES

PLAN OF THE STUDY

A double-blind, placebo-controlled trial was conducted in ECZTRA 6 to determine whether tralokinumab monotherapy could treat adolescents with moderate to severe AD. The first dose (double the following dose) followed by 16 weeks of subcutaneous tralokinumab or placebo was given to patients at week 0. Anatomical Therapeutic Chemical Classification System permitted rescue medication whenever needed. Maintenance treatment (75 or 150 mg) is given two to four weeks apart until week 52.

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A blinded placebo was given every two weeks to ensure that the primary goals of the study were achieved without the need for rescue medications. In those patients who were still on maintenance therapy, tralokinumab 150 mg every 2 weeks with low- to medium-potency TCI or TCS was switched to open-label treatment with tralokinumab after 2 weeks. We have treated all patients with tralokinumab, 150 mg, every 2 weeks for as long as they have recovered or lost their response to treatment with weak- to moderate-potency TCS or TCIs. Each relevant ethics committee and institutional review board has approved the study protocol (Supplement 2). In accordance with the laws, regulations, and guidelines specific to this country, a written protocol was followed for this trial. Informed consent forms were required for participants or the agents of their legal representatives. In accordance with CONSORT guidelines, it was reported.

Patients

The criteria for eligibility vary based on weight, the age of AD, or whether AD has been treated with TCS/TCI without success or what percentage of body surface area is affected by AD. Besides a score of 3 on the Investigator's Global Assessment (IGA) and if an individual scores four or more on the Worst Pruritus Numeric Rating Scale (NRS), A Numeric Rating Scale adolescent pruritus test should be conducted on adolescents to determine whether they are experiencing the worst pruritus.

End Points

Our primary endpoints were patients who achieved an IGA13 score of 0 (clear) or 1 (almost clear) by week 16 and those who improved 75% on the EASI12 by week 16. As part of the secondary end point, patients must achieve a change in Scoring AD (SCORAD) and change in Children's Dermatology Life Quality Index (CDLQI)15 from baseline to week 16. The change should be at least 4 on the Adolescent Worst Pruritus NRS (weekly average). Adolescents' understanding of pruritus was determined through the validation of the NRS with regulatory authorities. A secondary outcome measure was the difference between baseline and week 16 in EASI 50 and EASI 90. In addition to the Eczema-Related Sleep NRS, patients also reported symptoms on the Patient-Oriented Eczema Measure. Tralokinumab was administered as maintenance therapy for patients who achieved EASI 75 during week 16 and received IGA scores of 0 or 1. For weeks 50, 75, and 90, the IGA score for open-label endpoints was 0, 1, and 50, 75. There were a variety of adverse events and serious adverse events reported during the trial in terms of safety.

Statistical Analysis

144 were compared between tralokinumab and placebo for the primary endpoints. In the study, tralokinumab was given every two weeks at 150 mg, and the placebo at 75 mg. When comparing these two response rates, the power to detect a 20% difference at week 16 (summing the two-sided significance levels of 5.0% and 10%) was approximately 94%. As determined by EASI 75, tralokinumab, 75 mg, and placebo would be sufficiently significant at the 2-sided level at week 16 using different significance levels. A 92% power or higher is necessary to detect a difference.

A major event that could influence the effects of treatment was the initiation of treatment and the permanent discontinuation of treatment. Response rates after discontinuing treatment and withdrawing rescue medication were measured using a composite and for binary endpoints. We considered patients without data and those receiving rescue medication as non-responders. Using the IGAs and regions as baselines, we used the Cochrane–Mantel–Haenszel method to compare treatment groups. All patients were assumed to adhere to treatment regimens when assessing the treatment differences. A linear mixed-effects model was used to analyze the data after discontinuing treatment permanently or initiating rescue medication. In weeks 16 and 17, descriptive responses were described among those who had reached EASI 75 (overall group scores of 0 or 1) as well as those who had achieved IGA scores of 0 or 1. Both pooled and individual treatment arms were used to assess maintenance end points. Each treatment period was summarized with rescue medications and concomitant treatments. Three different analyses have been conducted to assess the safety of the product. All tests were conducted at a significance level of 5%.

Table 1: Analyze of Baseline Statistics and Demographics.

Feature	Total (N = 144)	Placebo (n = 48)	75 mg (n = 47)	150 mg (n = 49)
Indicators of age (IQR), year				
12-14	65	24	18	23
17-18	79	24	29	26
Average weight (IQR), in kg	58.0	58.0	59.5	58.0
Sexuality				
Female	70	21	24	25
Male	74	27	23	24
Average (IQR) length of AD, in	12.0	12.0	12.0	12.0

years				
Average (IQR), % of BSAs affected	48.0	51.0	48.0	43.0
Four out of five on the IGA	67	21	22	24
(IQR) Median EASI	27.0	26.1	27.8	27
Average (IQR) of SCORAD	65.8	65.6	64	67.2
Average (IQR) CDLQI	12	12	12	12
The average weekly median urticaria among adolescents (IQR)	7.7	6.5	6.8	6.1
Previously treated conditions	144	48	47	49
Corticosteroids applied topically	144	48	47	49
Anticalcineurin topical cream	84	28	26	30
Corticosteroids administered systemically	78	24	24	30
Immunosuppressants	30	10	11	9
(Unspecified type) monoclonal antibodies	3	1	1	1
Immunosuppressive medications	1	1	0	0
Wraps for wet items	38	14	13	11
Treatment with light	37	14	14	9
Complications				
only AD	18	5	5	8
≥1 Atopic disease comorbid with another disease	121	41	40	40
≥2 diseases associated with atopic eczema	98	34	35	29
Atopic diseases with 3 comorbidities	64	22	23	19

Table 2: Results of the Safety Analysis Set (N = 144) during the Initial Treatment Phase.

Outcome	**Placebo (n = 48)**	**75 mg (n = 33)**	**150 mg (n = 32)**
Patients with 1 adverse event	24	22	22
Diabetes Type I patients can die from adverse events	3	1	1
Adverse event intensity			
An ordinary cold	20	24	23
A medium level	15	16	16
Extreme	3	3	1
An investigational medicine-related adverse event	10	13	12
Withdrawal resulting from an adverse event	0	1	0
5% of all adverse events occurred in any group.			
Irritable bowel syndrome viral infection	4	9	6
A respiratory infection of the upper respiratory tract	2	4	5
Eczema atopica	6	7	3
Reactions at the site of injection	0	3	1
Insufficiency of oxygen	2	1	2
Anxiety	1	3	3
Event of particular interest when it comes to adverse outcomes			
Problems with the eyes	1	2	2
Glaucoma	1	2	1
Usually referred to as conjunctivitis	0	1	0
Infection of the conjunctiva with bacteria (preferred term)	0	0	1
Atopic conjunctivitis (preferable)	1	1	1
A viral conjunctivitis (more commonly known as conjunctivitis)	0	0	0
Skin rashes	1	1	1
Dermatitis herpetiformis	1	1	0

Cancerous tumors	0	0	0
A systemic treatment is required for skin infections	1	3	1
Reactions at injection sites	1	4	4

DISCUSSION

An 11-to-17-year-old children with moderate to severe AD was randomized to monotherapy with talokinumab. Talokinumab improved psychosocial and symptomatic effects of AD significantly compared to placebo at week 16 [7]. ECZTRA 1 and 2 monotherapy studies of adults operated at phase 3 did not achieve full clinical benefits for tralokinumab at week 16. By week 52, no rescue medication, including TCS [8, 9], was needed for the patients' clinical responses at week 16. Open-label tralokinumab, 150 mg, every 2 weeks, failed to meet either primary end point or required rescue therapy in one-third of patients, and over half scored 75 on EASI at week 52 after receiving tralokinumab, 150 mg, every 2 weeks, and failed to meet both primary end points. Patients in the adult study reached EASI 90 more often with the passage of time, as did the number reaching EASI 90 in a week [10].

To date, we have not found any studies showing that targeting IL-13 alone can improve symptoms of AD in a pediatric population, or improve outcomes in multiple high-effect diseases [11]. A majority of AD subtypes are expected to respond to tralokinumab, including pediatric patients, based on the preliminary data shown here from weeks 4 to 52 [12].

The laboratory parameters did not indicate that extra laboratory monitoring was needed due to the lack of clinical consequences associated with eosinophilia. Despite the fact that some patient-reported outcomes improved more with 150 mg than 75 mg of trasokinumab, every two weeks, both 75 mg and 150 mg of trasokinumab showed efficacy in both primary and secondary endpoints [13], and rescue medication was initiated later. Both doses had favorable safety profiles, with no effect on adverse events. There was no conjunctivitis (preferred term) with 75 mg or 150 mg of tralokinumab, while there was no exacerbation of disease with 150 mg [14]. Tranokinumab was also found to be safe and tolerable in adolescents.

AD treatments should be evaluated based on both clinical signs and patient-reported outcomes, particularly since the disorder impacts adolescents psychosocially [15]. A number of patient-reported outcomes have been demonstrated to improve with Tralokinumab, including sleep burden, pruritus, quality of life, anxiety, and depression.

At week 16, tralokinumab was efficacious, and it continued to be efficacious through week 52. The use of dupilumab for this age group has also proven to be highly effective [16]. Comparisons between trials are difficult because of changing patient reports of chronic disease outcomes would not be considered in studies with different study designs, analysis methods, or populations [17]. Tralokinumab decreased acne occurrence significantly less than Janus kinase inhibitors, too, in addition to its favorable safety profile [18]. In addition, tralokinumab significantly reduced rates of adolescent conjunctivitis [19]. The blocking of only IL-13 by tralokinumab resulted in a lower frequency of conjunctivitis than dupilumab, thus explaining why tralokinumab has been associated with a lower frequency of conjunctivitis than dupilumab.

CONCLUSIONS

Using tralokinumab monotherapy, adolescents with moderate to severe AD were shown to benefit from the treatment. Unfortunately, its use has been associated with serious side effects. Treatment was associated with few side effects, and anxiety, depression, and sleep disorders were not significant withdrawal symptoms. Adolescents with AD who took talokinumab also reported improvements in their sleep problems and itch problems. Tralokinumab has been shown to work effectively and well for adults with uncontrolled AD who have high levels of IL-13. There is increasing evidence that tralokinumab may be a safe and effective treatment for adolescents who suffer from uncontrolled AD.

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