SHORT COMMUNICATION

Real-Life Experience of Tralokinumab for the Treatment of Adult Patients with Severe Atopic Dermatitis: A Multicentric Prospective Study

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Abstract

Background Tralokinumab, the first fully human monoclonal antibody that binds specifically to interleukin-13, was safe and effective for treating atopic dermatitis (AD) in clinical trials, but real-life experience is still limited.

Objectives The objective of this study was to evaluate the effectiveness and safety of tralokinumab in severe AD in a real-life multicenter prospective cohort.

Methods Adult patients with severe AD were enrolled between January 2022 and July 2022 and received tralokinumab subcutaneously for 16 weeks. Objective and subjective scores were collected at baseline, weeks 6 and 16. Adverse events were reported throughout the study.

Results Twenty-one patients were included. An improvement of at least 75% on the Eczema Area and Severity Index (EASI 75) was achieved in 66.7% of patients at week 16. The median objective and subjective scores at week 16 were significantly ($p < 0.001$) lower than those at baseline. Combination with cyclosporine was sometimes necessary at the beginning of treatment, and addition of upadacitinib was required for some patients with very severe disease during the treatment. The most frequent adverse events were flares of eczema (23.8%) and reactions at injection site (19.0%). No cases of conjunctivitis were reported. Four patients (19.0%) discontinued treatment.

Conclusions Tralokinumab is an effective first-line biotherapy for severe AD. However, therapeutic response may be progressive. Safety data were reassuring. Atopic dermatitis flares or reactions at the injection site may lead to discontinuation of treatment. A history of conjunctivitis on dupilumab is not a contraindication to the initiation of tralokinumab.

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Key Points

Tralokinumab, a monoclonal antibody anti-interleukin-13 approved for the treatment of severe atopic dermatitis in adult patients, was effective and safe in clinical trials, but real-world data are limited.

Tralokinumab is effective; however, clinical response is sometimes progressive; an overlap with another classical immunosuppressive treatment might be necessary up to 12 weeks.

No cases of tralokinumab-induced conjunctivitis were reported.

1 Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease [1], with a prevalence of approximately 20% among children and between 7 and 14% in adults [2]. Atopic dermatitis can have a major impact on the quality of life and is often associated with several atopic and non-atopic comorbidities [3]. Moderate-to-severe disease activity is present in 20–30% of AD patients [4, 5], who often require systemic treatment. Recent advances made in the understanding of the pathophysiology of AD has led to the emergence of new immunotherapies for this patient population [6, 7], who represented a large group with an unmet need for long-term disease control.

Tralokinumab is the first fully human IgG4 monoclonal antibody that binds specifically to interleukin (IL)-13 with high affinity, preventing it from binding to both IL-13Rα1 and IL-13Rα2 [8]. After dupilumab, it is the second biologic approved for the treatment of severe AD in adult patients who are candidates for systemic therapy. Tralokinumab was effective and safe in clinical trials [9–11] but real-world data are still lacking.

The aim of this study was to assess the effectiveness and safety of tralokinumab in adult patients with AD in real-life daily clinical practice.

2 Patients and Methods

2.1 Study Design and Population

Between January 01 2022, and July 31 2022, we prospectively enrolled 21 adult patients (aged > 18 years) from Belgian academic and non-academic hospitals or private dermatology practices who had been diagnosed with AD according to the revised Hanifin and Rajka criteria [12]. The patients received tralokinumab for severe AD due to failure or contra-indication of a previous systemic treatment, according to the Belgian Early-Access Program set up during this period. A 600 mg induction dose of tralokinumab was injected subcutaneously at baseline, followed by 300 mg every 2 weeks. Any approved topical AD treatments (mainly topical corticosteroids and topical calcineurin inhibitors) were permitted as needed, as well as adjuvant systemic therapy. At baseline, general information was collected about patient's clinical history, demographic data, characteristics of AD including history of previous systemic treatments, as well as atopic and non-atopic comorbidities. Atopic dermatitis severity was evaluated at baseline, at Week (W) 0 and W16. Effectiveness of treatment on the objective symptoms of AD was evaluated with the Eczema Area and Severity Index (EASI) and SCORing Atopic Dermatitis (SCORAD), and effectiveness on the subjective symptoms evaluated with SCORAD and the Peak Pruritus Numeric Rating Scale (PP-NRS). Quality of life improvement was measured by Dermalogy Life Quality Index (DLQI), and long-term disease control was measured with RECap for AtoPic eczema (RECAP).

This study and data collection were conducted with the approval of the hospital and faculty institutional review board (Commission d'Ethique Biomédicale Hospitalo-Facultaire) of Université catholique de Louvain (UCLouvain), Belgium. Informed consent was obtained from all study participants.

2.2 Study Outcomes

The primary outcome was defined as a 75% improvement in EASI (EASI 75) from baseline to W16. Secondary outcomes were the improvement in EASI, SCORAD, DLQI, PP-NRS and RECAP from baseline to W16. Additional outcomes included the median percentage change of EASI, SCORAD, DLQI, PP-NRS and RECAP between W0 and W16; the proportion of patients achieving a 50% or 90% improvement (from baseline to W16) in EASI (EASI 50 and EASI 90, respectively); and/or 50%, 75% or 90% improvement in SCORAD (SCORAD 50, SCORAD 75, SCORAD 90, respectively).

2.3 Statistical Analyses

The comparison between the EASI, SCORAD, DLQI, PP-NRS and RECAP scores from baseline and W16 was performed using a Wilcoxon signed-rank test. Comparison in effectiveness, safety, route of administration and overall satisfaction, evaluated by Likert scales, was performed using the same statistical method. All statistical analyses were performed with R version 4.1.1. The threshold for statistical significance was set at $p < 0.05$.

2.4 Safety

Safety was evaluated by reporting and monitoring the type, the incidence and severity of any adverse event (AE) occurring during the treatment period, and if it had led to treatment interruption.

2.5 Satisfaction with the Treatment

Likert scale surveys were used to assess the patient's and the physician's satisfaction regarding the effectiveness, safety, and route and frequency of administration. The overall satisfaction of the patient and physician was also evaluated.

All surveys are included in supplemental data.

3 Results

3.1 Baseline Characteristics

The study population included 21 patients from 6 dermatology departments and 2 private practices throughout Belgium (Table 1). Before starting tralokinumab, 12 (57.1%) patients were immunomodulator-naïve. Six patients were shifted directly from dupilumab—2 for recalcitrant conjunctivitis and 4 for ineffectiveness. Three patients were inadequately controlled with Janus-kinase inhibitor(s) (JAKi).

3.2 Tralokinumab Effectiveness

Regarding the primary outcome, 14 of 21 (66.7%) patients had achieved EASI 75 at W16 (Table 2).

For the secondary outcomes, the median $\pm$ interquartile range (IQR) of all scores at W16 were significantly lower than those at baseline (EASI 1.8 ± 6.1 vs 17.6 ± 15.9, $p = 6.41\mathrm{e}{-}05$; SCORAD 25.1 ± 18.8 vs 58.9 ± 21.8, $p = 3.21\mathrm{e}{-}04$; PP-NRS 3.0 ± 4.0 vs 8.0 ± 1.0, $p = 3.27\mathrm{e}{-}04$; DLQI 2.0 ± 9.0 vs 12.0 ± 10.0, $p = 3.83\mathrm{e}{-}04$; RECAP 4.5 ± 10.0 vs 21.5 ± 8.25, $p = 2.27\mathrm{e}{-}04$) (Fig. 1).

Tralokinumab reduced the severity of AD (Fig. 2) and enhanced patients' quality of life as demonstrated by the median percentage change $\pm$ IQR in EASI (-85.2 ± 19.2), SCORAD (-64.7 ± 37.3) and DLQI (-75.0 ± 73.3) from baseline. At W16, the median percentage change $\pm$ IQR in PP-NRS was -57.1 ± 50.0, compared with baseline. Tralokinumab also improved long-term disease control, as shown by a median percentage change of -71.7 ± 61.0 from baseline, in the RECAP score.

At W16, 10 of 25 (47.6%) patients achieved SCORAD 50, 5 (23.8%) achieved SCORAD 75 and no patients achieved SCORAD 90. Of the 21 patients, 16 (76.2%) achieved EASI50 and 6 (28.6%) achieved EASI 90.

Cyclosporine had to be maintained in four patients during the first weeks of treatment due to slow clinical improvement. Complete withdrawal was achieved after a median duration $\pm$ IQR of 12 ± 4 weeks. Upadacitinib was added in two patients during treatment: one patient with very severe and recalcitrant AD, insufficiently controlled after 12 weeks of tralokinumab associated with cyclosporine; and one patient with inadequately controlled disease at W16 of tralokinumab. Systemic corticosteroids were needed for a patient with an AD flare at W12.

At W16, median percentage changes $\pm$ IQR of EASI and SCORAD, respectively, were -86.5 ± 13.3 and $-66.5 \pm$

Table 1 Demographics and clinical characteristics of patients included in the study ($n = 21$)

Variable	Value
Median age, years ($\pm$ IQR)	43 ($\pm$ 24)
Sex, female, n (%)	12 (57)
Ethnicity	
Caucasian (white European), n (%)	18 (85.7)
Other, n (%)	3 (14.3)
Body mass index, kg/m^2	26.6 ($\pm$ 5.4)
Educational level, years of full-time education, n (%)	
< 9	2 (9.5)
9	1 (4.8)
< 11	1 (4.8)
12	3 (14.3)
> 12	13 (61.9%)
Missing, n (%)	1 (4.8%)
Smoking status, n (%)	
Current	6 (28.6%)
Former	4 (19.0%)
Never	11 (52.4%)
Alcohol use, >0 g/days	10 (47.6%)
Atopic dermatitis factor	
Age of onset, n (%)	
Infant	13 (61.9%)
Child	3 (14.3%)
Teenager	3 (14.3%)
Adult	2 (9.5%)
Localization, n (%)	
Diffuse	18 (85.7%)
Head and neck	4 (19.0%)
Flexural	3 (14.3%)
Nummular	1 (4.8%)
Prurigo	1 (4.8%)
Evolution, n (%)	
Flare-ups	9 (42.8%)
Continuous disease	12 (57.2%)
Scores at baseline, median ($\pm$ IQR)	
SCORAD	58.9 ± 21.8
EASI	17.6 ± 15.9
DLQI	12 ± 10.0
PP-NRS	8 ± 1.0
RECAP	21.5 ± 8.25
Previous topical treatments for atopic dermatitis, n (%)	
Emollients	21 (100.0%)
Topical corticosteroids	21 (100.0%)
Topical immunomodulators	15 (71.4%)
Previous systemic treatments for atopic dermatitis, n (%)	
Corticosteroids	10 (47.6%)
Cyclosporine	20 (95.2%)
Phototherapy	13 (61.9%)
Methotrexate	2 (9.5%)
Azathioprine	1 (4.8%)

Table 1 (continued)

Variable	Value
Dupilumab	6 (28.6%)
Janus-kinase inhibitors	3 (14.3%)
Upadacitinib	1 (4.8%)
Baricitinib	2 (9.5%)
Medical history	
Atopy, *n* (%)	
Allergic asthma	12 (57.1%)
Allergic rhinitis	12 (57.1%)
Allergic conjunctivitis	9 (42.8%)
Food allergy	6 (28.6%)
Viral infections, *n* (%)	
Recurrent or disseminated HSV	5 (23.8%)
HZV	2 (9.5%)

DLQI Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *HSV* Herpes simplex virus, *HZV* Herpes zoster virus, *IQR* interquartile range, *PP-NRS* peak pruritus numeric rating scale, *RECAP* RECap for AtoPic eczema, *SCORAD* SCORing Atopic Dermatitis

8.6 in immunomodulator-naïve patients, -82.35 ± 15.0 and -79.3 ± 42.3 in patients shifted from dupilumab, and -47.9 ± 35.5 and -48.9 ± 17.0 in those shifted from a JAKi.

3.3 Tralokinumab Safety

At least one AE occurred in 11 of the 21 (52.4%) patients; however, no serious AEs were reported. The most frequent AE was flare of AD (23.8%) (Table 3). Of the two patients with dupilumab-associated conjunctivitis, one did not relapse with tralokinumab and the other remained unchanged. No cases of new-onset conjunctivitis or respiratory tract infection were observed during this 16-week study. One patient was diagnosed with meningioma, discovered in the course of an amnesic stroke at W6. After 16 weeks of treatment, four patients (19.0%) had stopped tralokinumab—two for lack of effectiveness and two for important and invalidating reactions at injection site.

3.4 Satisfaction with the Treatment

Concerning satisfaction with the effectiveness of tralokinumab at W16, the median $\pm$ IQR was 5.7 (/7) $\pm$ 1.5 and 6.0 (/7) $\pm$ 1.7 for patients and physicians, respectively. The median $\pm$ IQR for the satisfaction about the safety at W16 was 3.7 (/5) $\pm$ 1.6 and 6.5 (/7) $\pm$ 2.2 for patients and physicians, respectively.

The route and frequency of administration did not appear to be an issue for the patients, as evidenced by a score of 5.0 (/5) $\pm$ 1.5 at W16 (median $\pm$ IQR).

Patients' overall satisfaction with tralokinumab treatment at W16 was 6.0 (/7) $\pm$ 1.25 (median $\pm$ IQR).

In the patient group, there was no significant difference between baseline and W16 regarding effectiveness, safety, route of administration and overall satisfaction. The physicians' satisfaction regarding safety significantly decreased between baseline and W16 ($p = 0.008$) (data not shown).

4 Discussion

In this Belgian prospective multicentric study, we present real-life data from 21 severe AD patients treated with tralokinumab. For the majority of patients, AD signs, symptoms and quality of life significantly improved after 16 weeks of treatment, as measured by both the objective and the subjective scores.

The 21 patients in this cohort were slightly ($\pm$ 10 years, median) older than those in previous clinical trials [10, 11] with a small predominance of female patients. Clinical scores at baseline were also lower than those in the clinical trials for SCORAD, EASI and DLQI, but were similar for PP-NRS. Other characteristics were comparable to those of clinical trials in terms of disease duration, atopic comorbidities, and morphology. For comparative reasons, we chose to evaluate the same primary endpoint (EASI 75 at W16) as used in the clinical trials.

At W16, 66.7% of patients in this cohort had reached EASI 75, which is more than in the ECZTRA3 and ECZTRA7 trials (56.0% and 64.2%, respectively). However, some patients required combined systemic therapy with cyclosporine (at beginning of treatment) or upadacitinib (during treatment), which was generally not allowed in clinical trials. If we exclude these patients, the number of patients reaching EASI 75 at W16 is slightly lower than in clinical trials (EASI 75 at W16 drops to 52.4%). This suggests that combination with another systemic treatment is sometimes necessary, especially at the beginning, but sometimes also during treatment. However, combination of immunosuppressive agents could possibly enhance the rate of opportunistic infections and other AEs.

The prognosis in terms of improvement in disease severity (median percentage change of EASI and SCORAD) was better in patients who were naïve of immunomodulatory treatments. Patients with recalcitrant disease, inadequately controlled with a previous biotherapy and/or JAKi, showed poorer responses. Patients with the least improvement were those who shifted to tralokinumab after lack of response to JAKi. This implies that for patients with difficult-to-treat AD, tralokinumab may probably not be the treatment of choice.

One study limit is mainly the follow-up duration. EASI 75 response rate continued to improve beyond W16 in the

Table 2 Primary and secondary outcomes at weeks 6 and 16

Outcome	Baseline	Week 6	Week 16	p value[a]
EASI 75, n (%)		8 (38.1)	14 (66.7)	
EASI 75, in patients without AST, n (%)		6 (28.6)	11 (52.4)	
EASI 75, in patients without AST nor AD flare, n/N (%)		4/14 (28.6)	7/14 (50.0)	
EASI, median ± IQR	17.6 ± 15.9	5.1 ± 5.7	1.8 ± 6.1	< 0.001
SCORAD, median ± IQR	58.9 ± 21.8	31.6 ± 18.0	25.1 ± 18.8	< 0.001
PP-NRS, median ± IQR	8 ± 1.0	4 ± 3.0	3.0 ± 4.0	< 0.001
DLQI, median ± IQR	12 ± 10.0	4 ± 5.0	2.0 ± 9.0	< 0.001
RECAP, median ± IQR	21.5 ± 8.25	8 ± 8.75	4.5 ± 10.0	< 0.001
Median percentage change[b] ± IQR in EASI			−85.2 ± 19.2	
Median percentage change ± IQR in SCORAD			−64.7 ± 37.3	
Median percentage change ± IQR in PP-NRS			−57.1 ± 50.0	
Median percentage change ± IQR in DLQI			−75.0 ± 73.3	
Median percentage change ± IQR in RECAP			−71.7 ± 61.0	
Patients naive of immunomodulators				
Median percent change ± IQR in EASI			−86.5 ± 13.3	
Median percent change ± IQR in SCORAD			−66.5 ± 8.6	
Patients shifted from dupilumab				
Median percent change ± IQR in EASI			−82.35 ± 15.0	
Median percent change ± IQR in SCORAD			−79.3 ± 42.3	
Patients shifted from JAK inhibitors				
Median percentage change ± IQR in EASI			−47.9 ± 35.5	
Median percentage change ± IQR in SCORAD			−48.9 ± 17.0	
EASI 50, n (%)		16 (76.2)	16 (76.2)	
EASI 90, n (%)		3 (14.3)	6 (28.6)	
SCORAD 50, n (%)		10 (47.6)	10 (47.6)	
SCORAD 75, n (%)		3 (14.3)	5 (23.8)	
SCORAD 90, n (%)		0 (0.0)	0 (0.0)	

AD atopic dermatitis, *AST* adjuvant systemic therapy (i.e., cyclosporine at beginning of treatment and/or upadacitinib during treatment), *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *EASI 50* EASI score improvement of at least 50%, *EASI 75* EASI score improvement of at least 75%, *EASI 90* EASI score improvement of at least 90%, *HSV* Herpex Simplex Virus, *HZV* Herpes Zoster Virus, *IQR* interquartile range, *PP-NRS* peak pruritus numeric rating scale, *RECAP* RECap for AtoPic eczema, *SCORAD* SCORing Atopic Dermatitis, *SCORAD 50* SCORAD score improvement of at least 50%, *SCORAD 75* SCORAD score improvement of at least 75%, *SCORAD 90* SCORAD score improvement of at least 90%

[a]Compared with Wilcoxon signed-rank test

[b]The median percentage change ± IQR was defined as the median of the percentage of change in EASI (or SCORAD or PP-NRS or DLQI or RECAP) from baseline to 16 weeks calculated for each patient

ECZTRA3 trial (up to 70% of patients at W32) and the clinical response was maintained at W32 in patients who achieved response at W16. The real-life use of tralokinumab is still too premature to compare with the 2-year data from ECZTEND [13] but our 16-week study provided encouraging data regarding long-term disease control.

When compared to real-life studies of similar duration (±16 weeks) with dupilumab, results for our patient cohort were better in terms of percentage change in EASI [14–16]. This contradicts two previous network meta-analyses of systemic treatments for AD [17, 18], which placed dupilumab as a more effective biotherapy than tralokinumab for the improvement of EASI. Combination with other classical immunosuppressive treatment, like cyclosporine, during the first weeks in some patients, probably explained these better results with tralokinumab. Also, in comparison with real-life dupilumab studies, our results were similar for improvement of DLQI, but less effective for reduction of PP-NRS.

As for the safety of tralokinumab, we reported fewer AEs than in trials (52.4% vs 65.7% in a pooled safety analysis of five randomized, double-blind, placebo-controlled Phase II and Phase III trials [19], and 77.5% in ECZTRA7). However, the higher rates of AD flares (23.8%) and reactions at injection site (19%), compared to trials, were responsible for a significant difference in physicians' perception of
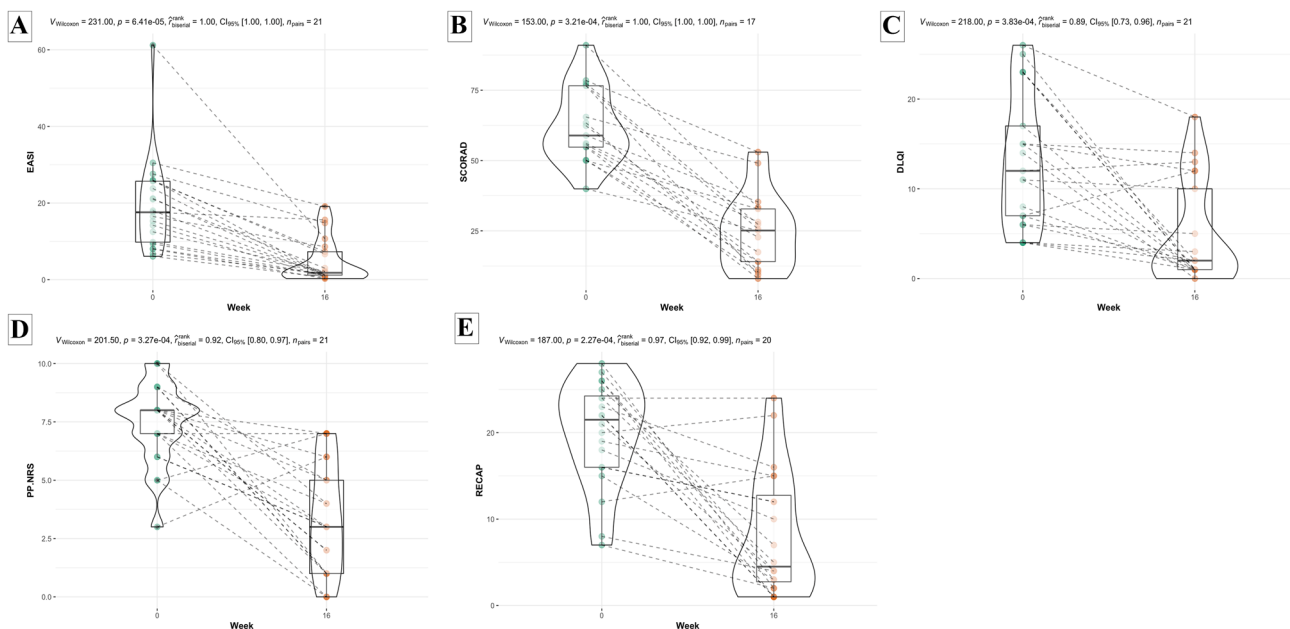
Fig. 1 Differences between baseline and week 16 for EASI (**A**), SCORAD (**B**), DLQI (**C**), PP-NRS (**D**), RECAP (**E**) for each patient (each colored dot), illustrated in boxplots. Each boxplot graphically represents the distribution of each quantitative variable (scores) by displaying minimum, maximum, first/third quartiles and median (bold line). The width of the box is proportional to the number of patients with the same score value. Statistical significance (P) is evaluated using pairwise Wilcoxon signed-rank test (V = statistical value of the test). *CI* confidence interval of rank biserial correlation, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *PP-NRS* peak pruritus numeric rating scale, *RECAP* RECap for AtoPic eczema, *SCORAD* SCORing Atopic Dermatitis

Baseline
EASI score = 9.8
SCORAD score = 54.92
DLQI score = 6
PP - NRS score = 6
RECAP score = 16

Week 16
EASI score = 2.1
SCORAD score = 17.44
DLQI score = 5
PP - NRS score = 3
RECAP score = 12

Fig. 2 Example of clinical improvement from baseline to week 16 in a patient receiving tralokinumab, topical corticosteroids and cyclosporine during the first weeks of treatment (complete cyclosporine withdrawal was achieved by week 10). *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *PP-NRS* peak pruritus numeric rating scale, *RECAP* RECap for AtoPic eczema, *SCORAD* SCORing Atopic Dermatitis

Table 3 Adverse events reported with tralokinumab (anti-interleukin-13) in real-life conditions in severe atopic dermatitis (21 adult patients over 16 weeks)

Adverse events	n (%)
At least one adverse event	11 (52.4)
Atopic dermatitis flare	5 (23.8)
Injection-site reaction	4 (19.0)
Weight gain	1 (4.8)
Meningioma	1 (4.8)
Conjunctivitis	0 (0.0)
Adverse event leading to discontinuation of treatment	4 (19)

treatment safety between W6 and W16, and a much higher percentage of patients stopping the treatment because of AEs (19% vs 2.4% in ECZTRA3 and 0.7% in ECZTRA7). These local reactions did not seem to decrease over the course of this present study. However, their pathophysiological mechanism remains unclear. Interestingly, no cases of new-onset tralokinumab-induced conjunctivitis were observed. Of the two patients who responded well to dupilumab but had severe conjunctivitis [20], one had no recurrence of conjunctivitis after 16 weeks of tralokinumab, and in the other patient, conjunctivitis persisted but was not aggravated. In both patients, AD remained adequately controlled.

This study is limited by the small number of patients included. The lack of treatment-related conjunctivitis reported may simply reflect the limited number of study participants rather than a true negative signal.

5 Conclusions

In conclusion, this observational study showed significant improvements in patients with severe AD, treated with tralokinumab, confirming that this molecule can be considered as a first-line biotherapy for AD. This real-world setting highlighted that the initial response to treatment can sometimes be progressive and that a period of overlap with another systemic treatment (up to 12 weeks) is possibly necessary. However, tralokinumab may not be the first choice for patients with recalcitrant or difficult-to-treat AD (failure of a previous biotherapy or JAKi). Even if the safety profile is reassuring, side effects such as AD flares or injection-site reactions, for which the mechanism is still undetermined, may lead to discontinuation of treatment. A history of conjunctivitis on dupilumab is not a contraindication to the initiation of tralokinumab treatment.

These results highlight the importance of confronting clinical trials with real-life clinical data in the context of emerging immunomodulators in AD and further studies with longer follow-up periods are warranted.

Declarations

Conflict of interest Axel De Greef, Pierre-Dominique Ghislain and Marie Baeck disclose their past participation on the tralokinumab advisory board organized by LEO Pharma but declare that the current study was conducted in an independent manner. Pierre-Dominique Ghislain received consultancy fees for expert work in clinical trials with other drugs from LEO Pharma. Audrey Bulinckx, Alison Coster, Céline de Halleux, Thomas Damsin, Marie-Claude Jacobs, Erwin Suys and Samer Zoghaib disclose no conflict of interest.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval This study and data collection were conducted with the approval of the hospital and faculty institutional review board (Commission d'Ethique Biomédicale Hospitalo-Facultaire) of Université catholique de Louvain (UCLouvain), Belgium. All procedures in this study were in accordance with the 1964 Helsinki declaration (and its amendments).

Consent for participation/publication The patients in this manuscript have given written informed consent to participate and for publication of their case details.

Code availability Not applicable.

Authors contribution ADG: conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft, visualization; PDG: data curation, investigation, writing—review and editing, supervision; AB: investigation, data curation; AC: investigation, data curation; CdH: investigation, data curation; TD: investigation, data curation; MCJ: investigation, data curation; ES: investigation, data curation; SZ: investigation, data curation; MB: conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—review and editing, supervision.

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