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Tralokinumab treatment for patients with moderate-to-severe atopic dermatitis in daily practice

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Abstract

Background Evidence about tralokinumab treatment for moderate-to-severe atopic dermatitis (AD) in daily practice is limited.

Aim To report the first evidence, to our knowledge, from daily practice of treatment with tralokinumab in patients with AD.

Methods In this observational prospective study, patients with AD who received tralokinumab treatment in the context of routine care at the Erasmus Medical Centre were included between November 2021 and February 2022. This included 28 patients who had previously been treated with dupilumab, and 14 patients who had been treated with a Janus kinase inhibitor (JAKi). The Investigator's Global Assessment (IGA; 0–4) and the numeric rating scale peak pruritus during the past 7 days (NRS itch 7d: 0–10), adverse events and reasons for discontinuation were analysed. A good clinical response was defined as any decrease in IGA and NRS itch 7d and if a patient was satisfied with the treatment and wished to continue with therapy.

Results In total, 37 patients were treated with tralokinumab. Twenty-two (59%) patients showed a good response to tralokinumab treatment. Fifteen (41%) patients discontinued treatment because of inadequate AD control or adverse events. Treatment-related adverse events were mild in most patients. Half of the patients where treatment with dupilumab had failed had a good clinical response to tralokinumab.

Conclusions Tralokinumab was found to be effective in most patients in this cohort with difficult-to-treat, severe AD from daily practice. Interestingly, tralokinumab was also found to be effective in 50% of patients who had previously experienced insufficient response or adverse events with dupilumab treatment.

What is already known about this topic?

- Tralokinumab, an interleukin (IL)-13 inhibitor, has been shown to be an efficacious and safe treatment of moderate-to-severe atopic dermatitis (AD) in clinical trials.
- However, it is known that treatment response and patients' characteristics in clinical trials differ from daily practice.

What does this study add?

- This study presents the first daily practice experience, to our knowledge, with tralokinumab treatment in patients with moderate-to-severe AD.
- Tralokinumab was found to be effective in most patients in this real-world cohort.
- Tralokinumab was also found to be effective in 50% of patients that previously experienced insufficient response or adverse events with dupilumab.

Introduction

Atopic dermatitis (AD) is a heterogeneous and highly prevalent chronic inflammatory skin disease. AD is characterized by intense itch that can result in sleep loss, is associated with depression and has a major impact on quality of life.[1,2] The basic treatment includes avoiding triggers, use of moisturizers, topical corticosteroids and topical calcineurin inhibitors. If patients show inadequate response to topical treatments, systemic immunosuppressive therapy may be required to achieve adequate disease control. In most European countries ciclosporin (CsA) is the only registered conventional systemic immunosuppressant, but azathioprine, mycophenolic acid/mycophenolate mofetil and methotrexate may also regularly prescribed off-label, particularly so before the recent registration of targeted

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treatments, including biologics and Janus kinase inhibitors (JAKis).[3–6]

After registration of dupilumab in 2017, a second biologic, tralokinumab, was approved in June 2021 by the European Medicines Agency. Dupilumab blocks interleukin (IL)-4Rα, thereby inhibiting the effects of IL-4 and IL-13 whereas tralokinumab specifically inhibits IL-13.[7–9] Previous studies have shown that disease severity in AD is correlated with IL-13 expression levels in lesional skin. Furthermore, IL-13 seems to be the most prominent type 2 cytokine in the lesional skin of patients with AD.[10–14]

The phase III clinical trials ECZTRA 1 and 2 showed that tralokinumab monotherapy vs. placebo resulted in significant improvement in the Investigator's Global Assessment (IGA) score in the first 16 weeks of treatment: 15.8% vs. 7.1% in ECZTRA 1 and 22.2% vs. 10.9% in ECZTRA 2. Furthermore, tralokinumab was well tolerated and adverse events were limited.[15] However, efficacy reported in clinical trials might differ from effectiveness in daily practice. This may be the result of differences between clinical trials and daily practice. Clinical trials commonly include a 'washout period' for topical and systemic treatment. This results in the exclusion of patients with the most severe cases in clinical trials, for whom it is unacceptable to discontinue all treatments. In addition, the strict inclusion and exclusion criteria used in clinical trials usually result in relatively healthy patient populations that do not necessarily reflect the patients seen in daily practice (for example, regarding comorbidities and comedication). To get better insights into real-world experience with tralokinumab therapy for AD, there is a need for real-world observational studies.[16]

To our knowledge, this is the first study from daily practice about tralokinumab treatment in patients with moderate-to-severe AD.

Table 1 Demographics and baseline characteristics

Baseline characteristics	Value ($n=37$)
Male	17 (46)
Fitzpatrick	
I	0 (0)
II	27 (73)
III	2 (5)
IV	6 (16)
V	0 (0)
VI	2 (5)
Age at start tralokinumab, median in years (IQR)	31 (15–66)
Previous use of systemic immunosuppressive drugs	
Ciclosporin A	29 (78)
Methotrexate	10 (27)
Azathioprine	4 (11)
Mycophenolic acid/mycophenolate mofetil	6 (16)
Systemic corticosteroids	17 (46)
Dupilumab	28 (76)
Upadacitinib	4 (11)
Abrocitinib	4 (11)
Baricitinib	6 (16)
Previous ultraviolet therapy	11 (30)
Concomitant therapy (with tralokinumab)	
Ciclosporin	4 (11)
Abrocitinib	2 (5)
Systemic steroids (short courses of 2–4 weeks)	5 (14)

Results are *n* (%) unless otherwise indicated. IQR, interquartile range.

Patients and methods

Study design and patient population

A prospective, observational, single-centre cohort study was conducted. Between November 2021 and February 2022, all patients (aged ≥15 years) with moderate-to-severe AD who started tralokinumab in the context of standard care at the Department of Dermatology at the Erasmus Medical Center (Rotterdam, The Netherlands) were included. Patients were eligible for treatment with tralokinumab if treatment with a conventional systemic immunosuppressant (such as CsA, methotrexate) failed, or after treatment with dupilumab or a JAKi (abrocitinib, baricitinib, upadacitinib) had failed. Patients visited the outpatient clinic at baseline, after 4 weeks, 8 weeks, 12–16 weeks and every 3 months thereafter. Data were collected in the context of the 'Erasmus MC IMID Quality of Care Registry' (MEC-2017-1123; W18_097#18.123). At baseline, demographics and patient characteristics were recorded.

Thirty-seven patients with AD who started tralokinumab treatment were included in our cohort study. Median age was 31 years (IQR 15–66), 46% was male (17/37) and 73% (27/37) had Fitzpatrick skin type II. Most patients had previously been treated with systemic immunosuppressive drugs; CsA (29/37; 78%) and systemic steroids (17/37; 46%) being the most frequently used. Twenty-eight (76%) patients had previously been treated with dupilumab and six (16%) had previously been treated with baricitinib, four (11%) with upadacitinib and four (11%) with abrocitinib (Tables 1 and 2).

Treatment

Tralokinumab was injected subcutaneously at baseline (600 mg loading dose), and 300 mg tralokinumab every 2 weeks thereafter. Conventional systemic immunosuppressants were discontinued at start, or tapered during tralokinumab treatment, as we have previously described for dupilumab treatment.[17] During tralokinumab treatment, patients were allowed to continue using moisturizers, topical corticosteroids, topical calcineurin inhibitors and oral corticosteroids.

Outcome measures

Clinical examinations were completed by experienced investigators. At every visit, the IGA (0–4) for AD was used to score the physician-reported severity and the numeric rating scale peak pruritus during the past 7 days (NRS itch 7d: 0–10) was used to score the patient-reported outcome measure. These outcome measures are concordant with the core outcome set of the global Harmonising Outcome Measures for Eczema initiative.

A good clinical response was defined as any decrease in IGA and NRS itch 7d and a patient who was satisfied with the treatment and wished to continue with the therapy. As this was a pragmatic, daily practice study no strict cutoff values were used, and patient satisfaction was leading. In patients experiencing adverse events but showing good clinical response to a previous treatment, switching to tralokinumab did not necessarily have to result in improvement of clinician-rated and patient-reported outcome measures.

Table 2 Patient characteristics and outcome measures[a]

Patient, sex	Age at start, years	Duration, weeks	IGA at baseline	IGA at last review	NRS itch 7d at baseline	NRS itch 7d at last review	Previous systemic medication	Concomitant systemic medication	Adverse events	Reason for starting tralokinumab	Reason for discontinuing tralokinumab
1, F	15	89	2	1	4	3		–	–	PT	–
2, F	50	131	2	1		1	CsA; AZA; dupi	–	Conjunctivitis	PT, head/neck dermatitis with dupi	–
3, M	25	129	2	1	1	0	–	–	–	PT	–
4, F	47	129	2	2	5	5	–	–	Conjunctivitis	PT	–
5, M	20	105	3	2	5	1	CsA	–	–	PT	–
6, F	19	78	3	2	8	–	–	–	–	PT	–
7, M	17	73	4	3	4	2	–	–	–	PT	–
8, F	44	36	3	2	6	2	CsA; dupi	–	–	Dupi NCI	–
9, M	25	34	2	2	5	5	CsA; AZA; dupi	–	Mild head/neck dermatitis	Head neck/dermatitis with dupi	–
10, M	24	33	3	1	6	1	Dupi; bari	–	–	Dupi NCI	–
11, F	43	32	1	0	2	0	CsA; dupi	–	–	Head neck/dermatitis with dupi	–
12, M	27	31	3	1	8	1	CsA	–	–	CsA failure	–
13, M	36	31	2		2	1	CsA; MPA; dupi	Low-dose CsA	–	Conjunctivitis with dupi	–
14, M	58	30	1	1	2	1	CsA; MTX; dupi		Conjunctivitis	Dupi NCI + conjunctivitis with dupi	–
15, M	23	30	2	1	–	–	CsA; dupi; abro	Abro since start	–	Conjunctivitis with dupi	–
16, M	25	30	2	2	2	2	CsA; MPA; dupi	–	–	Conjunctivitis with dupi	–
17, F	39	29	3	2	6	4	CsA	–	–	CsA failure	–
18, M	32	28	2	2	7	6	CsA; MTX; dupi	CsA tapering since week 2	Conjunctivitis	Dupi NCI + conjunctivitis with dupi	–
19, F	31	27	4	3	8	5	CsA; dupi	–	Conjunctivitis	Conjunctivitis with dupi	–
20, M	54	25	3	0	2	2	CsA; AZA; MTX; dupi	–	–	Dupi NCI	–
21, F	57	23	2		8	8	CsA; MTX; dupi	–	–	Head/neck dermatitis with dupi	–
22, M	38	14	2	1	1	0	MTX, dupi	–	–	Head/neck dermatitis with dupi	–
23, F	29	D11	3	4	8	8	CsA; dupi	Systemic corticosteroids week 1	Conjunctivitis	Head/neck dermatitis with dupi	No clinical improvement
24, F	21	D15	3	4	8	9	CsA; MTX; MPA; AZA; dupi; upa; abro; bari	Systemic corticosteroid week 1 and week 13; start MTX week 12	–	Dupi NCI	No clinical improvement
25, F	43	D23	2	2	7	6	CsA; dupi	Tapering CsA until week 16	–	Head/neck dermatitis with dupi	No clinical improvement
26, F	66	D7	2	2	6	6	dupi	–	Conjunctivitis	Head/neck dermatitis with dupi + conjunctivitis with dupi	No clinical improvement

(*Continued*)

Table 2 (*Continued*)

Patient, sex	Age at start, years	Duration, weeks	IGA at baseline	IGA at last review	NRS itch 7d at baseline	NRS itch 7d at last review	Previous systemic medication	Concomitant systemic medication	Adverse events	Reason for starting tralokinumab	Reason for discontinuing tralokinumab
27, M	31	D1	3		9	–	CsA; MPA; upa; bari	Systemic corticosteroids week 1	Monoarthritis	Failure previous medication	Monoarthritis
28, F	20	D8	1	2	4	–	CsA; dupi; upa; abro	–	Conjunctivitis	Conjunctivitis with dupi	No clinical improvement
29, F	49	D14	2	2	–	10	CsA; MTX; MPA; dupi; abro	Systemic corticosteroids week 2	Conjunctivitis	Head/neck dermatitis with dupi	No clinical improvement
30, F	61	D16	2	2	–	7	CsA; dupi	CsA		Conjunctivitis with dupi	No clinical improvement
31, F	40	D8	3	4	10	8	CsA; MTX; dupi; bari	–	Conjunctivitis	Head/neck dermatitis with dupi	Blepharitis anterior
32, M	29	D20	2	2	2	8	CsA; dupi	–	Hair loss (alopecia areata)	Head/neck dermatitis with dupi	No clinical improvement
33, M	26	D14	4	4	–	3	CsA; MPA; dupi; upa; bari	Abro since week 12, admitted to hospital in week 14 for coal tar treatment	Hair loss (alopecia androgenetica)	Dupi NCI	No clinical improvement
34, F	28	D13	3	2	8	8	CsA; dupi	–	–	Dupi NCI	No clinical improvement
35, M	52	D10	1	2	0	8	CsA; dupi	–	–	Head/neck dermatitis with dupi + conjunctivitis with dupi	No clinical improvement
36, F	18	D12	3	2	9	8	CsA; MTX; dupi; bari	–	–	Dupi NCI	Painful injections
37, M	31	D36	2	4	7	10	CsA; MTX; dupi	–	–	Head/neck dermatitis with dupi + dupi NCI	No clinical improvement

abro, abrocitinib; bari, baricitinib; AZA, azathioprine; CsA, ciclosporin A; D, discontinued; dupi, dupilumab; F, female; IQR, interquartile range; M, male; MPA, mycophenolic acid; MTX, methotrexate; NCI, no clinical improvement; PT, post-trial; Q2W, every 2 weeks; upa, upadacitinib. [a]Dose of tralokinumab at last review 300 mg every 2 weeks for all patients.

Effect of treatment is shown as the median change in IGA and NRS itch 7d scores between baseline and the score at last review, with a maximum follow-up duration of 24 weeks. Potential drug-related adverse events were registered.

Results

Concomitant systemic therapy

Four patients (4/37; 11%) were using CsA when starting tralokinumab. Three patients discontinued CsA after slowly tapering the dose.[17] However, one patient was not able to discontinue CsA because of exacerbation of disease after dose reduction. Two patients were using abrocitinib when tralokinumab was started. One patient successfully discontinued abrocitinib, but tapering was not successful in one patient because of inadequate disease control after discontinuation of abrocitinib. Five patients used short courses (maximum of 4 weeks) of concomitant systemic steroids to achieve adequate disease control (Tables 1 and 2).

Restarting tralokinumab treatment

Seven (7/37; 19%) patients had previously been treated with tralokinumab in a clinical trial. Patients restarted tralokinumab treatment after at least 5 months without tralokinumab. Restarting tralokinumab was successful in all seven patients (Tables 1 and 2).

Patients previously treated with dupilumab

Twenty-eight patients (28/37; 57%) had previously been treated with dupilumab and had discontinued treatment because of no clinical improvement, adverse events or both (Table 1). Fourteen of these patients (50%) had a good response to tralokinumab treatment. Five patients that had discontinued dupilumab because of no clinical improvement (Table 2: patients 8, 10, 14, 18, 20), had clinical improvement with tralokinumab (50%). Five of the 10 patients (Table 2: patients 13, 15, 16, 18, 19) that discontinued dupilumab because of conjunctivitis, had a good response to tralokinumab without conjunctivitis. Four out of five patients that developed a head/neck dermatitis with dupilumab (Table 2: patients 2, 9, 11, 21, 22), had a good response to tralokinumab without a head/neck dermatitis.

Physician- and patient-reporting outcomes of tralokinumab treatment

Median IGA at baseline was 2 [interquartile range (IQR) 1–4], and median IGA at last review was still 2 (1–4) in the total patient population (Table 3). Median NRS itch 7d decreased from 6 (1–10) to 5 (3–10).

In the 22 (of 37; 59%) patients (patients 1–22 in Table 2) that were still using tralokinumab at last review, NRS itch 7d scores decreased from a median of 5 at baseline to 2 at last review. In these patients the median IGA was 2 at baseline and remained 2 at last review (Table 3, Figure 1).

Dose intervals

In one patient with inadequate disease control using dosing every 2 weeks dosing, tralokinumab was given 300 mg weekly, which resulted in a good clinical response. In four patients the dosing interval was extended to 300 mg every 3 weeks; in one 15-year-old female patient because of good response; and in three patients because of adverse events (for example, hair loss and conjunctivitis). These adverse events disappeared in two patients, but they discontinued tralokinumab treatment because of insufficient clinical improvement (Table 2).

Adverse events

Adverse events with tralokinumab treatment were mostly mild. Of 37 patients, 9 experienced conjunctivitis (24%), which was controlled with eye drops (lubricants and antihistamine eye drops). Two patients experienced hair loss (5%). One patient was diagnosed with alopecia areata that had started during his previous treatment with dupilumab, and persisted during treatment with tralokinumab. The other patient was diagnosed with androgenetic alopecia. One patient had a mild head/neck dermatitis (3%). In three patients, the adverse events were the reason for discontinuation of tralokinumab treatment, for example, a blepharitis anterior, monoarthritis and painful injections (Table 2) (discussed in further detail below).

Discontinuation of tralokinumab treatment

Fifteen out of 37 patients (41%) (nos 23–37 in Table 2) discontinued tralokinumab, after an average treatment duration of 14 weeks (range: 1–36 weeks). Twelve out of 15 patients (80%) discontinued tralokinumab because of no clinical improvement, of which 10 patients (10/12 83%) discontinued treatment before 16 weeks. Three patients (3/15; 20%) discontinued treatment because of adverse events. One patient discontinued tralokinumab after 8 weeks of treatment due to anterior blepharitis (diagnosed by an ophthalmologist). A 31-year-old man discontinued tralokinumab because of acute monoarthritis diagnosed by a rheumatologist, 1 week after the administration of the tralokinumab loading dose. Another patient, an 18-year-old woman discontinued because the injections were too painful (Table 2).

Table 3 Group-level outcome measures for participants treated with tralokinumab[a]

Patients	IGA at baseline	IGA at last review	NRS itch 7d at baseline	NRS itch 7d at last review
All patients	2 (1–4)	2 (1–4)	6 (1–10)	5 (3–10)
Responders	2 (1–4)	2 (1–3)	5 (1–8)	2 (0–8)
Nonresponders	3 (1–4)	2 (2–4)	7 (4–10)	8 (3–10)

Data are median (IQR). IGA, Investigator's Global Assessment (0–4); IQR, interquartile range; NRS itch 7d, numeric rating scale peak pruritus during the past 7 days (0–10). [a]Dose of tralokinumab at last review 300 mg every 2 weeks for all patients.

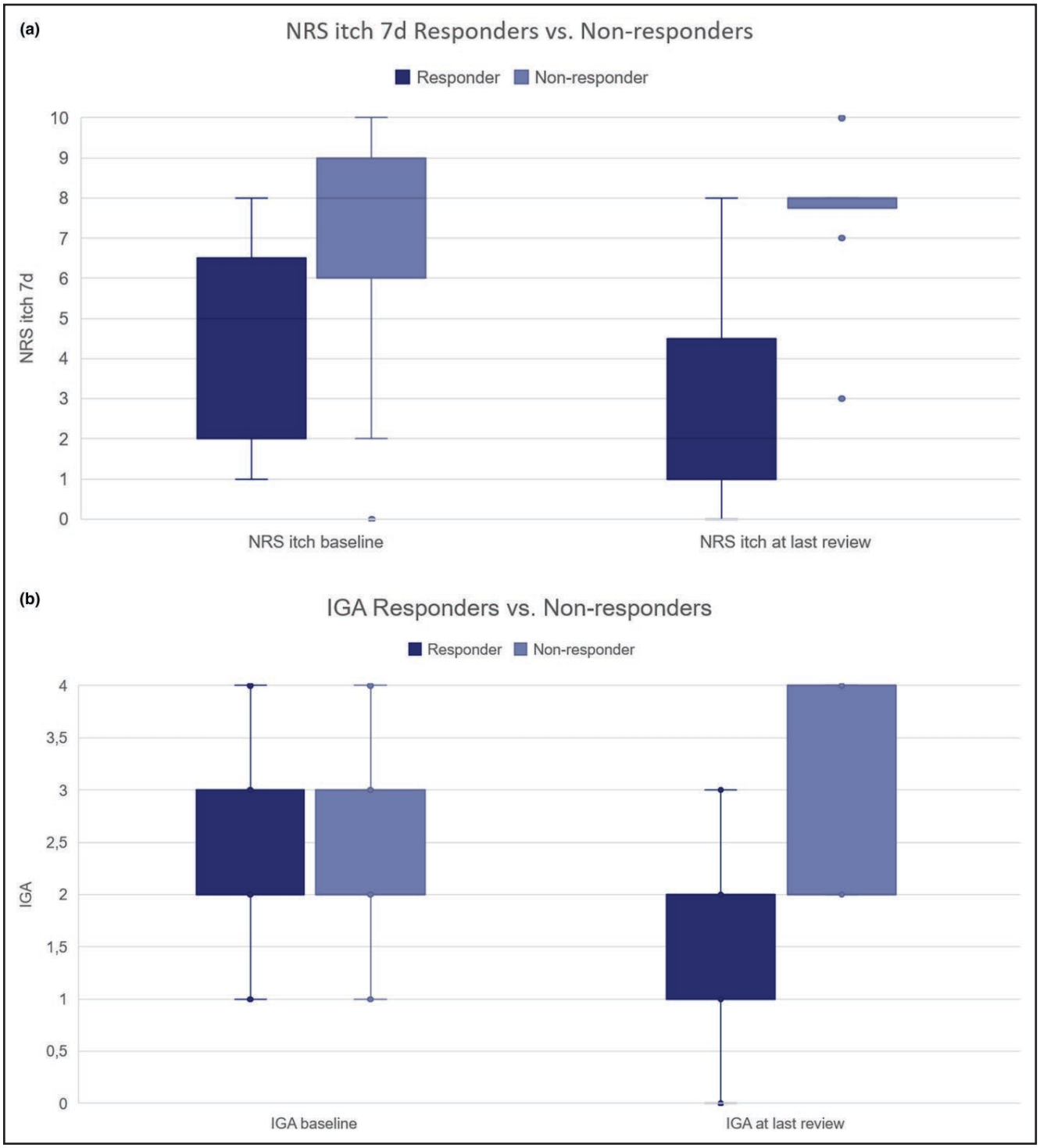

Figure 1 Disease severity in responders ($n=22$) vs. nonresponders ($n=15$). (a) Numeric rating scale peak pruritus during the past 7 days (NRS itch 7d, 0–10) responders vs. nonresponders; (b) Investigator's Global Assessment (IGA, 0–4) responders vs. nonresponders. Box: quartiles 1–3; vertical line in the centre of the box: median (μ); whiskers: minimum and maximum; dots: outliers.

Discussion

Until recently, therapeutic options for patients with moderate-to-severe AD were limited to conventional systemic immunosuppressants such as CsA. Other systemic immunosuppressants such as methotrexate and azathioprine were commonly used off-label. Recently, several new targeted therapies have become available, including biologics and JAKis. Although effectivity has been shown in clinical trials, real-world evidence on these new drugs is limited.[18,19] This is the first report, to our knowledge, providing real-world evidence for use of tralokinumab in patients with AD from daily practice.

In this study, 37 patients with AD treated with tralokinumab in daily practice were analysed. Based on treatment history, the patients in this real-world cohort can be considered as having severe, difficult-to-treat AD, as most have been treated with several conventional systemics and several had also failed dupilumab or a JAKi. Twenty-two patients experienced a good clinical response. In 15 patients, tralokinumab was discontinued, because of inadequate AD control ($n=12$) or adverse events ($n=3$) (Table 2).

The baseline characteristics of the patients included in this study are comparable with those in clinical trials for tralokinumab. However, the physician- (IGA) and patient-reported outcome (NRS itch 7d) scores in our patients were lower at baseline compared with patients in the clinical trials, which is probably a result of the washout periods for topical and systemic treatments in clinical trials resulting in worsening of the disease.[15,20] In addition, compared with patients in clinical trials, most of the patients in our cohort were previously treated with multiple systemic immunosuppressants, biologics and/or JAKis[21] (Table 1). We classify these patients as having severe, difficult-to-treat AD.

Evaluation of tralokinumab treatment effect is recommended after 16 weeks of treatment.[21] In our cohort, 10 out of 12 patients that discontinued tralokinumab treatment because of no clinical improvement, discontinued treatment before 16 weeks. This was mostly because patients did not experience any effect and were not willing to continue tralokinumab until at least 16 weeks of treatment (Table 2). Seven patients discontinued tralokinumab treatment and a restart was successful in all these patients. Although the number of patients is limited, it suggests that a temporary discontinuation of tralokinumab treatment and restart is possible.

Five of 10 patients who experienced insufficient effect with dupilumab treatment showed a good response to tralokinumab. Four of five patients that developed a head/neck dermatitis using dupilumab treatment showed improvement after switching to tralokinumab (Table 2). Five of the 10 patients that developed conjunctivitis during dupilumab treatment showed improvement after tralokinumab treatment. We therefore conclude that in at least 50% of patients who failed dupilumab, because of inefficacy or adverse events, tralokinumab may be an effective treatment option.

Tralokinumab is a fully human monoclonal antibody that specifically neutralizes the IL-13 cytokine, in contrast to dupilumab, which blocks the receptor for IL-4 and IL-13. As a subset of patients experienced insufficient response to dupilumab, but did show a response to tralokinumab we hypothesize that there may be different endophenotypes that respond differently to these drugs. Further research is needed to identify these underlying endophenotypes.

There are several limitations in this study. As tralokinumab was only recently registered for the treatment of AD, the number of patients is relatively small. All patients in this study had previously been treated with several conventional systemics and therefore represent a difficult-to-treat population. Future studies are needed to investigate the long-term effectiveness and safety of tralokinumab treatment in daily practice.

In conclusion, tralokinumab appeared to be effective in a subset of patients with severe AD that has not responded to several systemic treatments. Interestingly, in patients who had not responded to dupilumab treatment, tralokinumab was found to show a good response in about 50% of them.

Funding sources

None.

Conflicts of interest

D.J.H. is an investigator for AbbVie, Almirall, LEO Pharma, AstraZeneca, Novartis and Sanofi; consultancies for AbbVie, Sanofi, LEO Pharma, AstraZeneca, Novartis, Janssen, Pfizer and Lilly. The other authors declare they have no conflicts of interest.

Data availability

Data are available on request from the corresponding author.

Ethics statement

Ethical approval: Medical Research Ethics Committee MEC-2017–1123; W18_097#18.123. Informed consent: all patients gave written, informed consent for participation and publication of their case details and images.

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