Use of topical corticosteroids with tralokinumab in adult patients with moderate-to-severe atopic dermatitis: results from the 32-week, Phase 3 ECZTRA 3 trial

Jonathan I. Silverberg,[1] Andrew E. Pink,[2] Azra Kurbasic,[3] Christina Kurre Olsen,[3] Stephan Weidinger[4]

[1]Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA; [2]St. John's Institute of Dermatology, Guy's and St. Thomas' Hospitals, London, UK; [3]LEO Pharma A/S, Ballerup, Denmark; [4]Department of Dermatology and Allergy, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease[1,2] characterized by eczematous lesions and multiple symptoms including pruritus, sleep disturbance, and depression.[3–5] The type 2 cytokine, interleukin (IL)-13, is a key driver of the underlying inflammation of AD and is overexpressed in lesional and non-lesional AD skin[6,7]
- Depending on the severity of AD, topical corticosteroids (TCS) are recommended as a first-line pharmacological intervention; however, TCS alone are often inadequate for the treatment of moderate-to-severe AD and prolonged use of TCS may cause unwanted adverse effects[8,9]
- Tralokinumab, a first-in-class, fully human monoclonal antibody, is designed to neutralize IL-13, specifically inhibiting downstream IL-13 signaling and thereby preventing pro-inflammatory activity[6,7,10]
- The ECZTRA 3 trial (NCT03363854) evaluated the efficacy, safety, and use of tralokinumab plus TCS, compared with placebo plus TCS, in treating patients with moderate-to-severe AD for up to 32 weeks
  - Significantly more patients achieved the primary efficacy endpoints of an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) [IGA-0/1] and a 75% improvement in Eczema Area and Severity Index (EASI) [EASI-75], with tralokinumab every 2 weeks (q2w) plus TCS compared with placebo plus TCS during the initial 16 week treatment period[11]

Objective

- The objective of this analysis was to assess TCS use in patients with moderate-to-severe AD receiving tralokinumab combined with TCS in the ECZTRA 3 trial

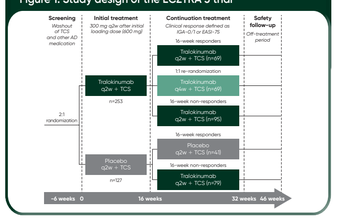
Methods

Patients

- Eligible patients were ⩾18 years of age with a confirmed diagnosis of AD for ⩾1 year and with an inadequate response to treatment with topical medications. Additional eligibility requirements included an AD body surface area involvement of ⩾10%, EASI score of ⩾12 at screening and 16 at baseline, and IGA score of ⩾3

Study design

Figure 1. Study design of the ECZTRA 3 trial



- Patients were randomized 2:1 to receive either subcutaneous tralokinumab 300 mg q2w plus TCS, after a 600 mg loading dose of tralokinumab, or placebo plus TCS over an initial treatment period of 16 weeks **(Figure 1)**
- At 16 weeks, tralokinumab responders (defined as being IGA-0/1 and/or EASI-75 responders at week 16) were re-randomized 1:1 to continuation treatment with tralokinumab q2w or every 4 weeks (q4w) plus TCS for an additional 16 weeks. Placebo responders continued with placebo plus TCS and all non-responders received tralokinumab q2w plus TCS for an additional 16 weeks

Concomitant TCS use during ECZTRA 3

- TCS (mometasone furoate, 0.1% cream, 180–200 g. Europe: Class 3 [potent]; USA: Class 4 [midstrength]) was supplied proactively from randomization to the end of treatment
- Throughout the entire treatment period, a thin film of the dispensed mometasone was applied by the patient once daily to active lesions as needed; patients were instructed to return used and unused tubes at each trial visit to allow measurement of the amount of TCS used
- TCS use was continually monitored for safety and appropriateness, and was discontinued gradually when control was achieved
- Lower-potency TCS or topical calcineurin inhibitors could be prescribed if needed on areas where the supplied TCS was inadvisable or on areas where continued treatment with TCS was considered unsafe

Endpoints

- Additional secondary endpoints assessed at week 16 were the amount of TCS used and the number of days without TCS use
- Continuation endpoints included IGA-0/1 at week 32 among patients with IGA-0/1 at week 16 and EASI-75 at week 32 among patients with EASI-75 at week 16, both after initial randomization to tralokinumab

Safety

- Adverse events assessments were performed at baseline and at each visit

Statistical analyses

- Primary endpoints for the initial 16-week treatment period were assessed using a hierarchical testing procedure and Holm–Bonferroni multiplicity adjustment
- The amount of TCS used and the number of days without topical treatment use were determined by a 2-week period and 1-week period, respectively. Each endpoint was analyzed by a repeated measurements model with an unstructured covariance matrix and the mean modelled as: Y = treatment*week + region + baseline IGA. Data observed after initiation of rescue treatment or after permanent discontinuation of investigational medicinal product (IMP) were excluded from the analyses
- IGA-0/1 and EASI-75 at week 32 were summarized using descriptive statistics
- Safety analyses were performed using the safety analysis set, with initial treatment and continuation treatment reported separately

Results

Patient characteristics

- A total of 380 patients were randomized to receive either tralokinumab q2w plus TCS (n=253) or placebo plus TCS (n=127) over the initial 16-week treatment period
- Baseline demographics and disease characteristics were similar across both treatment groups **(Table 1)**. All patients had received prior therapy, with almost all receiving TCS (98.2%); 61.1% had used systemic steroids, while cyclosporine was the most common prior oral immunosuppressant used (31.1%)

Table 1. Patient demographics and disease characteristics at baseline

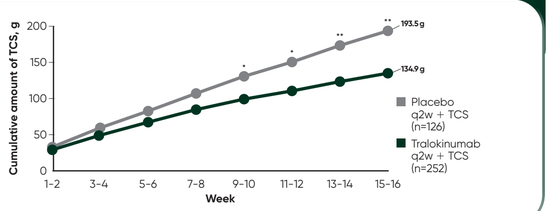
	Placebo + TCS (n=127)	Tralokinumab q2w + TCS (n=253)
Mean age, years	37.7	39.8
Male, n (%)	84 (66)	125 (49)
Mean duration of AD, years	28.7	28.0
Region, %		
North America[a]	42.5	41.9
Europe[b]	57.5	58.1
Mean BSA involvement with AD, %	49.0	47.6
Severe disease (IGA-4), %	4.7	4.6
Mean EASI	30.4	28.8
Mean weekly average worst daily pruritus NRS score	7.9	7.7
Mean SCORAD	68.9	67.0
Mean DLQI	17.2	17.6

DLQI, Dermatology Life Quality Index; NRS, Numerical Rating Scale; SCORAD, SCORing Atopic Dermatitis. [a]Includes USA and Canada; [b]Includes Belgium, Germany, Netherlands, Poland, Spain, and UK.

TCS use during the initial treatment period

- Cumulative TCS use was 30.3% lower at weeks 15 to 16 with tralokinumab (adjusted mean 134.9 g) versus placebo (adjusted mean 193.5 g; P=0.004) with separation observed from week 9–10 **(Figure 2)**

Figure 2. Cumulative TCS use through week 16



*P<0.05 versus placebo plus TCS; **P<0.01 versus placebo plus TCS.
Assuming no non-returned tubes were used. Data collected after permanent discontinuation of IMP or initiation of rescue medication not included. Repeated measurements model: TCS (g) = treatment*week + region + baseline IGA.

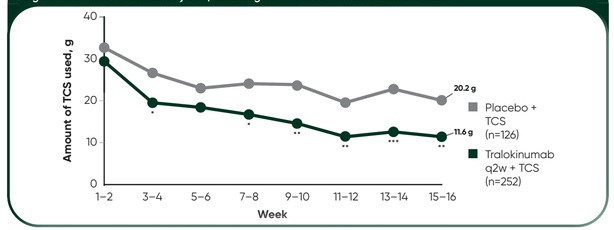
- Use of rescue treatment, which included higher potency TCS or systemic treatment for AD, was reported by 2.8% of patients in the tralokinumab q2w plus TCS group and 10.2% of those in the placebo plus TCS group **(Table 2)**

Table 2. Rescue medication use by type during the initial treatment period

Medication, n (%)	Placebo + TCS (n=127)	Tralokinumab q2w + TCS (n=253)
Any rescue medication	13 (10.2)	7 (2.8)
Topical		
Corticosteroids	10 (7.9)	5 (2.0)
Other	0	1 (0.4)
Systemic		
Corticosteroids	3 (2.4)	3 (1.2)
Immunosuppressants	3 (2.4)	0

- Mean compliance with returning of TCS tubes was similar in the tralokinumab q2w plus TCS group and the placebo plus TCS group (95.1% and 97.5%, respectively
- At weeks 15 to 16, patients in the tralokinumab group used approximately 50% less of the supplied TCS compared to patients who received placebo (tralokinumab, 11.6 g; placebo, 20.2 g; P=0.002) **(Figure 3)**

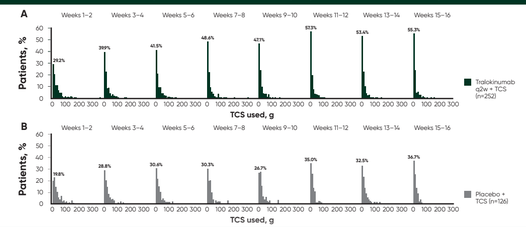
Figure 3. Amount of TCS used by visit, assuming no TCS used from non-returned tubes



Data collected after permanent discontinuation of IMP or initiation of rescue medication not included. Repeated measurements model. TCS amount (g) = Treatment*Week + Region + Baseline IGA.

- A greater proportion of patients used <5 g of TCS at week 15 to 16 with tralokinumab (55.3%) versus placebo (36.7%) **(Figure 4)**

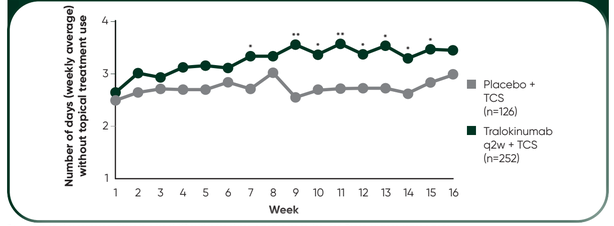
Figure 4. Distribution of TCS use by visit (A) for tralokinumab q2w plus TCS and (B) placebo plus TCS



Assuming no TCS used from the non-returned tubes.

- The number of days without topical treatment was slightly higher in patients treated with tralokinumab plus TCS compared to the placebo group during the initial treatment period, with separation observed at week 7 and from week 9 to week 15, respectively (P<0.05) **(Figure 5)**

Figure 5. Days without topical treatment use (weekly average) during the initial treatment period

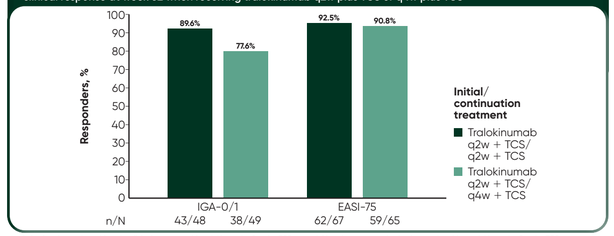


Data collected after permanent discontinuation of IMP or initiation of rescue medication not included. Repeated measurements model: Number of days (weekly average) = Treatment*Week + Region + Baseline IGA.

TCS use during the continuation treatment period

- At week 32, 89.6% and 92.5% of patients treated with tralokinumab q2w plus TCS and 77.6% and 90.8% of patients treated with tralokinumab q4w plus TCS, who responded to tralokinumab q2w plus TCS treatment at week 16, maintained an IGA-0/1 and EASI-75 response, respectively **(Figure 6)**

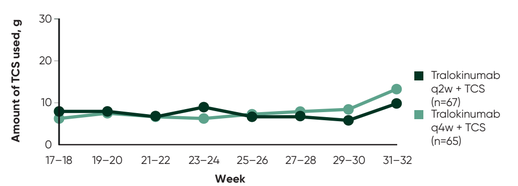
Figure 6. Proportion of tralokinumab q2w plus responders (IGA-0/1 and EASI-75) at week 16[a] who maintained their clinical response at week 32 when receiving tralokinumab q2w plus TCS or q4w plus TCS



[a]Analysis of patients who achieved a clinical response with tralokinumab q2w plus TCS at week 16 and were re-randomized to receive either tralokinumab q2w plus TCS or tralokinumab q4w plus TCS until week 32.

- The high level of maintained response at week 32 with tralokinumab q2w or q4w in patients who achieved EASI-75 at week 16 was not associated with an increased use of TCS **(Figure 7)**

Figure 7. TCS use in patients receiving tralokinumab q2w or q4w during the continuation period (week 16 to 32) who achieved EASI-75 at week 16 without rescue medication



The amount of TCS used by visit, assuming no TCS used from the non-returned tubes. Repeated measurements model: Change = Treatment*Week + Baseline*Week + Baseline IGA. No statistically significant differences were observed at any time point.

- In patients who did not respond to tralokinumab q2w plus TCS at week 16 and then continued with tralokinumab q2w plus TCS treatment up to week 32, TCS use increased from 13.8 g at week 16 to 15.0 g at week 32 (data not shown)
- TCS use decreased from 25.4 g to 16.3 g between weeks 16 and 32 in placebo non-responders who were assigned to tralokinumab q2w plus TCS at week 16 (data not shown)

Safety

- Tralokinumab in combination with TCS was well tolerated in patients with moderate-to-severe AD **(Table 3)**
- The safety profile at week 32 was comparable with the initial 16-week treatment period

Table 3. Summary of adverse events in the initial 16-week treatment period[a]

Week 16, n (%)	Placebo + TCS (n=126)	Tralokinumab q2w + TCS (n=252)
At least one AE	84 (66.7)	180 (71.4)
At least one serious AE	4 (3.2)	2 (0.8)
AE leading to withdrawal from the trial	1 (0.8)	5 (2.0)
Frequent AEs (≥5% in any treatment group)[b]		
Viral upper respiratory tract infection	14 (11.1)	49 (19.4)
Conjunctivitis	4 (3.2)	28 (11.1)
Upper respiratory tract infection	6 (4.8)	19 (7.5)
Injection site reaction	0	17 (6.7)
Atopic dermatitis	10 (7.9)	6 (2.4)
Headache	6 (4.8)	22 (8.7)

[a]Preferred terms according to Medical Dictionary for Regulatory Activities, version 20.0.

Conclusions

- Tralokinumab 300 mg q2w plus TCS was significantly more efficacious than placebo plus TCS at treating moderate-to-severe AD
- The lower use of TCS by tralokinumab-treated patients compared to placebo-treated patients through the initial 16-week treatment period, and the lower use of rescue medication in the tralokinumab arm, demonstrated the potential steroid-sparing effects of tralokinumab
  - By week 16, TCS use was 50% higher for placebo compared to tralokinumab, suggesting the observed high placebo response could be attributed to high TCS use
  - For comparison, the level of TCS use (38.1 g/month)[12] reported in a recent prescription database study in patients with moderate-to-severe AD was similar to that seen in the placebo-treated patients presented here
- The reduction in TCS use is important because prolonged use of TCS is associated with unwanted adverse events, especially in patients concomitantly receiving other forms of corticosteroids,[8] reflecting the "real-world" setting

References

1. Nutten S. Ann Nutr Metab 2015; 66(Suppl 1): 8–16. **2.** Weidinger S, Novak N. Lancet 2016; 387: 1109–1122. **3.** Eckert L et al. J Am Acad Dermatol 2017; 77: 274–279e272. **4.** Silverberg JI et al. Ann Allergy Asthma Immunol 2018; 121: 340–347. **5.** Dalgard FJ et al. J Invest Dermatol 2015; 135: 984–991. **6.** Bieber T. Allergy 2020; 75: 54–62. **7.** Tsoi LC et al. J Invest Dermatol 2019; 139: 1480–1489. **8.** Eichenfield LF et al. J Am Acad Dermatol 2014; 71: 116–132. **9.** Bogaviewicz M et al. J Allergy Clin Immunol Pract 2017; 5: 1519–1531. **10.** Popovic B et al. J Mol Biol 2017; 429: 208–219. **11.** Weidinger S et al. Oral presentation at the American Academy of Dermatology Virtual Meeting, 2020. **12.** Choi JY et al. Br J Dermatol 2020; 182: 1017–25.

Disclosures

The tralokinumab ECZTRA 3 study was sponsored by LEO Pharma. Jonathan I. Silverberg has received honoraria as a consultant/advisory board member from LEO Pharma and acted as a consultant for, and/or received grants/honoraria from, AbbVie, Anaptysbio, Asana Biosciences, Lilly, Galderma Research and Development, GlaxoSmithKline, Glenmark Generics, Kiniksa, LEO Pharma, Medimmune, Menlo Therapeutics, Pfizer, PuriCore, Regeneron, and Sanofi. Andrew E. Pink has acted as an advisor/speaker for AbbVie, Almirall, Janssen, La Roche-Posay, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi, and UCB. Azra Kurbasic, and Christina Kurre Olsen are employees of LEO Pharma. Stephan Weigindor has received honoraria as an advisory board member/speaker from AbbVie, Lilly, La Roche-Posay Laboratoire Pharmaceutique, LEO Pharma, Novartis, Sanofi Genzyme, and Sanofi/Regeneron, received fees as an investigator from AbbVie, Almirall, Lilly, LEO Pharma, Pfizer, and Sanofi-Genzyme, and received grants/research funding from La Roche-Posay Laboratoire Pharmaceutique, LEO Pharma, and Novartis.

2020 Fall Clinical Dermatology Conference, October 29-November 1, 2020, Live Virtual Meeting