revealed by hair analysis. Environ Int 2018;121:1341–54.

Pellerin L, Henry J, Hsu CY, Balica S, Jean-Decoster C, Méchin MC, et al. Defects of filaggrin-like proteins in both lesional and nonlesional atopic skin. J Allergy Clin Immunol 2013;131:1094–102.

Sakabe J, Yamamoto M, Hirakawa S, Motoyama A, Ohta I, Tatsuno K, et al. Kallikrein-related peptidase 5 functions in proteolytic processing of profilaggrin in cultured human keratinocytes. J Biol Chem 2013;288:17179–89.

Song XF, Chen ZY, Zang ZJ, Zhang YN, Zeng F, Peng YP, et al. Investigation of polycyclic aromatic hydrocarbon level in blood and semen quality for residents in Pearl River Delta Region in China. Environ Int 2013;60:97–105.

EASI p-EASI: Predicting Disease Severity in Patients with Atopic Dermatitis Treated with Tralokinumab

JID Open

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TO THE EDITOR

Numerous targeted treatments for atopic dermatitis (AD) are currently under investigation in clinical trials. Comparability of the efficacy of new drugs is therefore becoming more and more important. However, this remains challenging given the high intra-observer and interobserver variability of primary endpoints (Flohr, 2011). The use of serological biomarkers may overcome this problem. Recent studies have shown that a combination of serum biomarkers, including TARC, IL-22, and sIL-2R (using a formula called predicted Eczema Area Severity Index [EASI] [p-EASI]), predicts disease severity in patients with AD treated with dupilumab, cyclosporine A, and topical corticosteroids (Bakker et al., 2020; Thijs et al., 2019, 2017). The advantage of the use of serum biomarkers is that they are objective and do not require subjective assessment of disease activity by clinicians (Renert-Yuval et al., 2021). This study reports on the use of p-EASI in a randomized controlled trial with tralokinumab treatment. The safety and efficacy of tralokinumab in AD have been shown in several clinical trials.

A total of 198 adult patients with moderate-to-severe AD were randomly included from the total population of the ECZema TRAlokinumab Trial No. 1 trial (N = 802) (NCT03131648). Written informed consent was obtained from all participants, and the trial was approved by the ethics committee of the Medical Faculty at the Ludwig-Maximilian University of Munich (Munich, Germany) (Wollenberg et al., 2021).

Baseline characteristics were well-balanced across treatment and placebo groups (Supplementary Table S1). A total of 149 patients were treated with subcutaneous 300 mg tralokinumab every other week, and 49 patients received a placebo for 16 weeks. If medically necessary (e.g., intolerable AD symptoms), rescue treatment for AD was provided at the discretion of the investigator. Disease severity was assessed by EASI, and serum was collected before initiation of treatment (time 0) and after 16 weeks of treatment (time 3). Serum TARC, sIL-2R, and IL-22 levels were measured using a multiplex immunoassay, as previously described (Bakker et al., 2020; Thijs et al., 2019, 2017). Differences between the two time points were tested by Wilcoxon signed-rank tests. All patients provided informed consent.

Tralokinumab treatment significantly decreased median EASI scores from baseline (30.9, interquartile range [IQR] = 22.5–42.3) through week 16 (13.5, IQR = 6.6–22.5, $P < 0.0001$). At week 16, the median percentage changes from baseline in the levels of TARC measured were significantly larger in the tralokinumab-treated patients than in the placebo-treated group (Figure 1). The largest difference was observed for TARC levels in tralokinumab versus placebo (−57.01% vs. −28.33%, $P = 0.0007$). The levels of sIL-2R (−32.28% vs. −29.06%, $P = 0.33$) and IL-22 (−23.63% vs. −24.98, $P = 0.94$) showed comparable decreases in both groups (Figure 1 and Supplementary Table S2).

Serum biomarker levels were used to calculate p-EASI scores at two time points using the formula: $b_{0t} + b_{1t} \times \log(\text{TARC}) + b_{2t} \times \text{IL-22} + b_{3t} \times \text{sIL-2R}$ (Thijs et al., 2017), a linear combination of biomarkers with coefficients that can vary over the treatment course. p-EASI is an algorithm to evaluate severity on the basis of serum markers rather than a static formula. At time point t, the coefficients are estimated that can vary over the treatment course. Application of this algorithm on datasets with different ranges in EASI and biomarkers (values that are not limited to a certain maximum) will generate different coefficients. In addition, the output of p-EASI is not constrained to the range of EASI (0–72). Therefore, we proposed a translation factor with the existing data to facilitate its use in clinical practice. Consequently, p-EASI can be compared across different studies by mapping its value into the same range of EASI.

The EASI and p-EASI scores showed a moderate correlation (Spearman correlation r = 0.59, $P < 0.0001$). In patients

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area Severity Index; IQR, interquartile range; p-EASI, predicted Eczema Area Severity Index; sIL-2R, soluble IL-2 receptor

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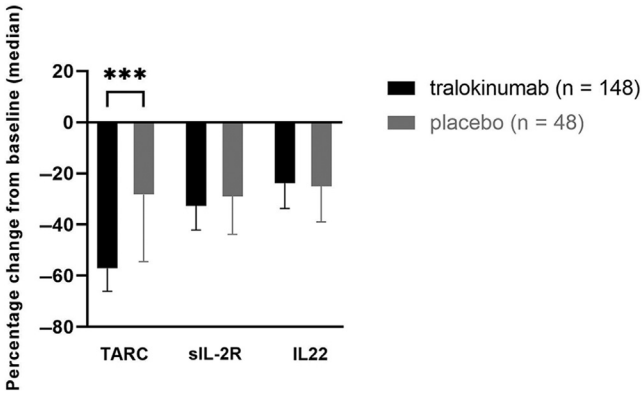

Figure 1. Median percentage (IQR) change from baseline to week 16 in biomarker levels. Significance levels correspond to the following *P*-value: ***$P = 0.0007$. IQR, interquartile range.

treated with tralokinumab, median EASI and p-EASI decreased from 30.9 (IQR = 22.5–42.3) and 32.9 (IQR = 25.6–40.2) to 13.5 (IQR = 6.6–22.5) and 24.8 (IQR = 20.6–59.0), respectively, after 16 weeks of treatment. In the placebo group, median EASI and p-EASI were 31.1 (IQR = 22.5–40.4) and 31.3 (IQR = 25.0–37.5), respectively, at baseline and 19.0 (IQR = 10.2–29.1) and 29.2 (IQR = 25.5–32.5) after 16 weeks of treatment (Figure 2).

Tralokinumab treatment resulted in a large decrease in serum TARC levels, but the effect on the levels of IL-22 and sIL-2R were similar for both groups. This is in accordance with a previous study that showed significant effects of dupilumab treatment on TARC and IL-22 levels but no significant change in sIL-2R levels (Bakker et al., 2020). This suggests that different treatments may have differential effects on the individual components of the p-EASI signature. Although the use of a combination of biomarkers may not be essential for all treatments, an affordable, standardized assay that can be used for all treatments may be preferable over different combinations of biomarkers for specific treatments and therefore contribute to improving the comparability of study outcomes.

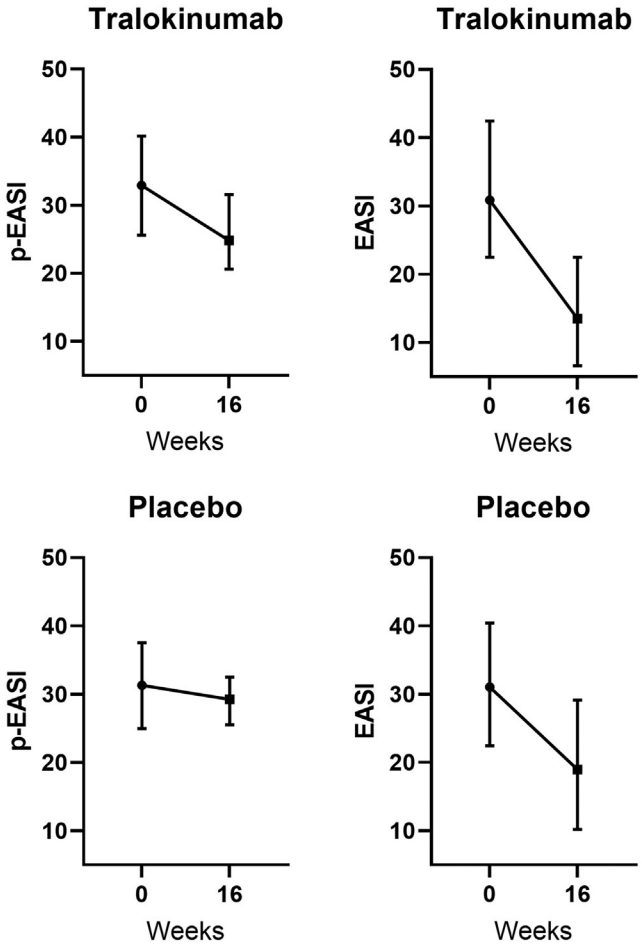

Figure 2. Median EASI and p-EASI scores in 149 patients with AD at baseline (week 0) and after 16 weeks of tralokinumab treatment versus 49 patients with AD receiving placebo. Error bars represent the interquartile range. AD, atopic dermatitis; EASI, Eczema Area Severity; p-EASI, predicted Eczema Area Severity.

The effects on serum biomarker levels in the placebo group might be explained by the use of rescue therapy (e.g., topical steroids) that was allowed at the discretion of the investigator during the trial. The previous cohort included patients with AD treated with topical corticosteroids once daily and showed significant effects on TARC, sIL-2R, and IL-22 levels (Thijs et al., 2017).

Patients in the placebo group only showed small changes in p-EASI compared with patients treated with tralokinumab (Figure 2). The effect on EASI scores in patients treated with placebo was higher than the effect on p-EASI. Because p-EASI is a truly objective measure, this suggests that the effect on EASI in the placebo group may be an overestimation of the real biological effect.

This may be the result of two phenomena that have been reported in clinical trials, including eligibility creep and regression to the mean. Eligibility creep suggests an overestimation of disease severity at inclusion (eligibility screening) (Hick and Feldman, 2007; Leshem et al., 2019). The outcome measures (e.g., EASI) for assessing disease severity have subjectivity to them. Therefore, when there is a range of scores that are subjectively reasonable, the observer might lean toward the high end of the subjective range at initial visits. Scoring in the middle of the subjective range during subsequent visits would yield an apparent improvement in the placebo group, resulting in regression to the mean.

Our study was limited by the absence of diversity in ethnicity, and representation of patients with black skin is lacking. In addition, children were not included in this study. Furthermore, the clinical significance of p-EASI remains undefined. Additional research is needed to correlate clinical important outcome measures such as EASI50/EASI75. This study shows that the use of a biomarker signature (p-EASI) reflects disease severity in patients with AD treated with tralokinumab in a clinical trial setting. We suggest that the use of objective biomarker signatures such as p-EASI is essential to objectively assess treatment effects and allow for comparison of new drugs for the treatment of AD.

Data availability statement

All data generated or analyzed during this study are included in this published article and its Supplementary Materials and Methods.

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CONFLICT OF INTEREST

MAR is an employee of LEO Pharma A/S. JCDR is a former employee of LEO Pharma A/S. DJH is an investigator for AbbVie, Galderma, LEO Pharma, MedImmune/AstraZeneca, Novartis, and Sanofi/Regeneron and is a consultant for Incyte, Janssen, LEO Pharma, Lilly, MedImmune/AstraZeneca, Novartis, and Pfizerand Regeneron/Sanofi. The remaining authors state no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: JIO, LEMDW, MAR, JCDR, DJH; Data Curation: JIO, LEMDW, MAR, JCDR; Formal Analysis: JIO, MAR, JCDR, DJH; Funding Acquisition: MAR, DJH; Investigation: JIO, LEMDW, WAD, DJH; Methodology: JIO, MAR, JCDR, DJH; Project Administration: JIO, LEMDW, MAR, DJH; Resources: MAD, WAD, DJH; Supervision: MAR, DJH; Validation; JIO, MAR, JCDR, DJH Visualization: JIO, LEMDW, MAR, DJH; Writing – Original Draft Preparation: JIO, LEMDW, DJH; Writing – Review and Editing: JIO, LEMDW, MAR, WAD, JCDR, DJH

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2022.06.008

REFERENCES

Bakker DS, Ariens LFM, Giovannone B, Hijnen D, Delemarre EM, Knol E, et al. EASI p-EASI: predicting disease severity in atopic dermatitis patients treated with dupilumab using a combination of serum biomarkers. Allergy 2020;75:3287–9.

Flohr C. Atopic dermatitis diagnostic criteria and outcome measures for clinical trials: still a mess. J Invest Dermatol 2011;131:557–9.

Hick J, Feldman SR. Eligibility creep: a cause for placebo group improvement in controlled trials of psoriasis treatments. J Am Acad Dermatol 2007;57:972–6.

Leshem YA, Bissonnette R, Paul C, Silverberg JI, Irvine AD, Paller AS, et al. Optimization of placebo use in clinical trials with systemic treatments for atopic dermatitis: an International Eczema Council survey-based position statement. J Eur Acad Dermatol Venereol 2019;33:807–15.

Renert-Yuval Y, Thyssen JP, Bissonnette R, Bieber T, Kabashima K, Hijnen D, et al. Biomarkers in atopic dermatitis-a review on behalf of the International Eczema Council. J Allergy Clin Immunol 2021;147:1174–90.e1.

Thijs JL, Drylewicz J, Bruijnzeel-Koomen CAFM, Giovannone B, Knol EF, de Bruin-Weller MS, et al. EASI p-EASI: predicting disease severity in atopic dermatitis patients treated with cyclosporin A. Allergy 2019;74:613–7.

Thijs JL, Drylewicz J, Fiechter R, Strickland I, Sleeman MA, Herath A, et al. EASI p-EASI: utilizing a combination of serum biomarkers offers an objective measurement tool for disease severity in atopic dermatitis patients. J Allergy Clin Immunol 2017;140:1703–5.

Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021;184:437–49.

Genetic Architectures Underlie Onset Age of Atopic Dermatitis

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TO THE EDITOR

Genetic attributions for age of onset have been investigated for multiple entities (Blauwendraat et al., 2019; Kamboh et al., 2012; Power et al., 2017; Woolston et al., 2017), but evidence is still lacking in allergic diseases. Wan et al. (2017) found that *FLG* mutations are associated with earlier atopic dermatitis (AD) onset. Ferreira et al. (2020) performed a GWAS for allergic diseases, including AD, supporting the notion of strong genetic effects on early- and late-onset AD. These are the only studies that have

Abbreviation: AD, atopic dermatitis

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Supplementary Table S1. Baseline Characteristics

Characteristics	Placebo (n = 49)	Tralokinumab Q2W (n = 149)
Female sex, n (%)	12 (24.5)	49 (32.9)
Age, median (IQR)	37 (27–46)	35 (27–46)
Race, n (%)		
White	32 (65.3)	112 (75.2)
Black	1 (2.0)	1 (0.7)
Asian	16 (32.7)	34 (22.8)
Other	0 (—)	2 (1.3)
Missing	0 (—)	0 (—)
EASI, median (IQR)	31.1 (22.5–40.4)	30.9 (22.5–42.3)
IGA score of 4, n (%)	26 (53.1)	81 (54.5)
SCORAD score, median (IQR)	69.8 (64.3–83.5)	70.7 (63.2–79.7)
POEM score, median (IQR)	24.0 (22.0–26.0)[1]	24.0 (19.0–27.0)[2]

Abbreviations: EASI, Eczema Area Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; SCORAD, SCORing Atopic Dermatitis.
[1]n = 1 missing value.
[2]n = 3 missing values.

Supplementary Table S2. Serum TARC, sIL-2R, and IL-22 Levels at Baseline and after 16 Weeks of Treaptment

Serum biomarkers	Values	Tralokinumab Q2W (n = 149)	Placebo (n = 49)
Serum TARC (pg/ml)	Baseline median value (IQR)	1,289.10 (411.94–3,175.18)	1,123.92 (358.78–2,923.83)
	Median value at 16 weeks (IQR)	347.46 (154.49–982.75)	653.36 (346.94–1,285.39)
	Median change from baseline (IQR)	579.94[1] (129.09–1,959.50)	130.00[1] (−89.32 to 1,205.99)
	Median percentage change from baseline (IQR)	−57.01[1] (−80.49 to −34.59)	−28.33[1] (−66.74 to 6.40)
Serum IL-22 (pg/ml)	Baseline median value (IQR)	65.78 (23.06–137.82)	58.48 (14.95–182.67)
	Median value at 16 weeks (IQR)	41.78 (11.39–100.01)	26.26 (9.70–99.30)
	Median change from baseline (IQR)	11.69[1] (−1.01 to 63.29)	10.27[1] (0.00–58.68)
	Median percentage change from baseline (IQR)	−23.63[1] (−56.26 to 1.03)	−24.98[1] (−62.03 to 0.00)
Serum sIL-2R (pg/ml)	Baseline median value (IQR)	770.33 (375.05–1,682.31)	754.87 (421.23–1,328.48)
	Median value at 16 weeks (IQR)	465.29 (195.00–929.44)	556.00 (263.56–898.79)
	Median change from baseline (IQR)	280.77[1] (0.00–660.34)	152.00[1] (0.00–389.28)
	Median percentage change from baseline (IQR)	−32.28[1] (−60.31 to 0.00)	−29.06[1] (−50.72 to 0.00)

Abbreviations: IQR, interquartile range; Q2W, every 2 weeks; sIL-2R, soluble IL-2 receptor.
[1]n = 1 missing value.