Received: 20 May 2020 | Revised: 19 June 2020 | Accepted: 6 July 2020

DOI: 10.1111/all.14492

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

LETTER TO THE EDITOR

EASI p-EASI: Predicting disease severity in atopic dermatitis patients treated with dupilumab using a combination of serum biomarkers

To the Editor,

During the past decade, new more targeted therapies for the treatment of atopic dermatitis (AD) have been developed and are currently under investigation in clinical trials. However, the comparison of results from different clinical studies remains challenging, given the substantial variation in clinician-rated outcome measures that are currently used, and high inter- and intra-observer dissimilarities.[1] An objective and consistent outcome measurement is hence needed to successfully compare different treatment options. Serum thymus and activation-regulated chemokine (TARC/CCL17) is currently the best performing objective biomarker for disease severity in AD.[2] Nevertheless, the correlation with disease severity is not strong enough to replace clinical outcome measures. Therefore, we previously proposed to use a biomarker combination reflecting different underlying pathways and showed that a biomarker signature including TARC, soluble interleukin (IL)-2-receptor (sIL-2R), and IL-22 was a significantly better predictor of disease severity than a single biomarker.[3] All three biomarkers have been reported to contribute to AD pathogenesis. TARC is a T-cell attracting chemokine, involved in T-cell recruitment to the skin,[3] sIL-2R is a proven marker of T-cell activation in vivo,[4] and IL-22 induces keratinocyte proliferation and inhibits terminal differentiation, thereby promoting epidermal hyperplasia and barrier defects.[5] Since the model was developed to predict Eczema Area and Severity Index (EASI) scores, this objective outcome measure was named "the predicted-EASI" (p-EASI). The p-EASI was developed using data of AD patients treated with topical corticosteroids (TCS) and recently validated in cyclosporin A (CsA) treated AD patients.[6] In the near future, novel immune-modulating drugs will transform the management of moderate-to-severe AD. Therefore, we aim to validate the p-EASI in patients treated with dupilumab, the first human monoclonal antibody-based treatment approved for adults with moderate-to-severe AD.[7]

We included 25 adult patients with moderate-to-severe AD from a previously published prospective cohort[8] (median age 32, IQR 27-49, 15 male, Table S1). Patients using oral immunosuppressive drugs within two (fast-acting) or four (slow-acting) weeks before baseline were excluded. Patients were treated with dupilumab 600 mg at initiation followed by 300 mg every other week for 16 weeks. Disease severity was assessed by EASI score, and serum was collected before initiation of dupilumab treatment (t_0) and after eight (t_1), twelve (t_2), and sixteen (t_3) weeks of treatment. Serum TARC, sIL-2R, and IL-22 levels were measured via Luminex-based multiplex immunoassays using an in-house validated panel of analytes, as previously described.[3,6] Differences between time points were evaluated by Wilcoxon matched-pairs signed-rank test. Patients signed Institutional Review Board-approved written consent, adhering to the Declaration of Helsinki Principles.

Dupilumab treatment significantly decreased median EASI scores from baseline (19.3, IQR 14.2-24.5) through week 8 (median EASI 5.2, IQR 2.4-8.0, $P < .0001$), week 12 (3.8, IQR 2.1-6.6, $P < .0001$), and week 16 (median EASI 3.9, IQR 2.4-7.6, $P < .0001$). Median serum TARC and IL-22 levels significantly decreased from t_0 to t_1 and remained stable onwards until t_3 (Figure 1). No significant change in median serum sIL2r levels was observed during the 16 weeks of dupilumab treatment.

Serum biomarker levels were used to calculate the p-EASI scores at the different time points using the following previously published signature[3]: *(−36.12 + 18.49*logTARC + 0.009*IL-22-0.009*sIL-2R)*(1-treatment)+(−5.82 + 4.04*logTARC + 0.003*IL-22-0.003*sIL-2R)*treatment*, in which treatment refers to dupilumab treatment, and can be either *No = 0*, or *Yes = 1*. The observed and predicted-EASI scores showed a high correlation (Spearman correlation $r = .67$, $P < .0001$). Median EASI and p-EASI were 19.3 (IQR 14.2-24.5) and 17.3 (IQR 8.5-20.2), respectively, before treatment, 5.2 (IQR 2.4-8.0) and 2.8 (IQR 1.6-3.9) after 8 weeks, 3.8 (IQR 2.1-6.6) and 2.7 (IQR 1.7-4.0) after 12 weeks, and 3.9 (IQR 2.4-7.6) and 3.1 (IQR 1.9-4.0) after 16 weeks of dupilumab treatment (Figure 2). Additionally measured biomarkers (Table S2) were not considered to have added value over the current signature, based on correlation with disease severity.

The current study demonstrates that the p-EASI corresponds closely to disease severity in AD patients before and after 8-16 weeks of dupilumab treatment. In comparison with our previous TCS and CsA treated AD cohorts, the correlation between EASI

Judith L. Thijs and Julia Drylewicz these authors contributed equally.

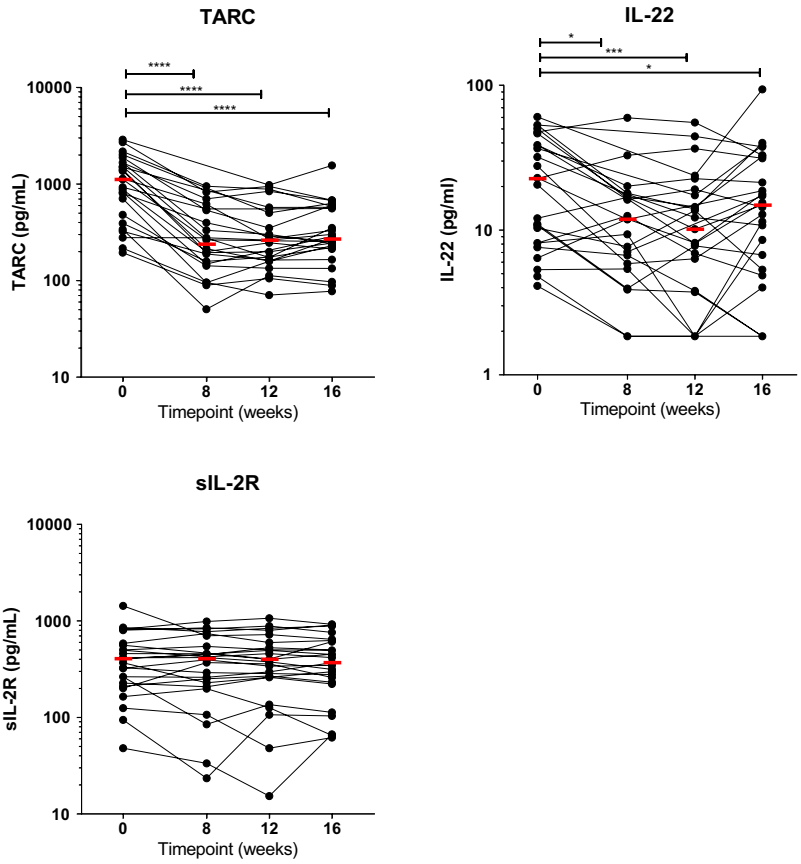

FIGURE 1 Serum TARC, IL-22, and sIL-2R levels from 25 AD patients before initiation of dupilumab treatment (week 0) and after 8, 12 and 16 wk of treatment. Red lines represent median. Significance levels correspond to the following *P* values: **P* < .05, ***P* < .01 and ****P* < .005

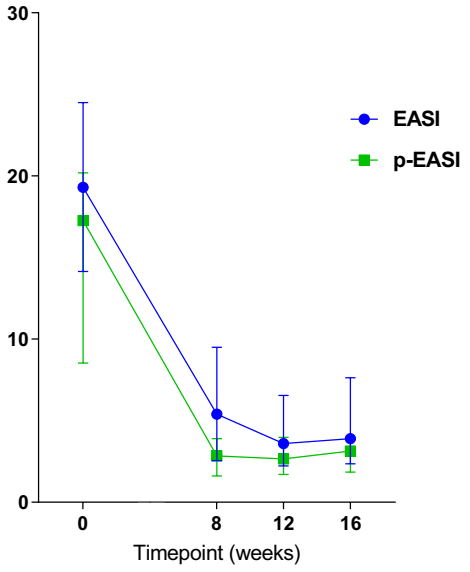

FIGURE 2 Median EASI and predicted-EASI (p-EASI) scores in 25 AD patients before initiation of dupilumab treatment (week 0) and after 8, 12 and 16 wk of treatment. Error bars represent interquartile range

and p-EASI was slightly lower in dupilumab treated AD patients. This may be explained by the sIL-2R levels remaining stable during dupilumab treatment, which was not observed in the other two cohorts. By targeting the IL-4Rα, dupilumab specifically inhibits the T helper (Th)2-related cytokines IL-4 and IL-13. Although sIL-2R is known to reflect T-cell activation and correlate to AD disease severity,[4,9] our results suggest that it is not influenced by dupilumab treatment. This might reflect that this biological only targets T-cell phenotypes directly involved in AD pathogenesis (Th2 cells). In comparison, CsA and, to a lesser amount, TCS have a broad systemic immunosuppressive effect, targeting multiple T-cell phenotypes and related cytokines. As few patients did show a quick drop in sIL-2R, extending the current model to a larger patient population including different phenotypes of AD might identify subtypes of AD patients in whom sIL-2R is an important marker.

The difference between EASI and p-EASI was larger at baseline and after 8 weeks of treatment, compared to the later time points. The difference at baseline might be explained by an overestimation of the EASI score due to a more severe disease at the moment of dupilumab initiation compared to the other time points. The EASI is a subjective score reflecting the visible skin lesions, while the p-EASI objectively reflects the extent and intensity of AD lesions, and might be ahead of clinical signs. Since dupilumab is a systemic immunomodulating drug, changes in serum biomarkers might occur before clinical signs improve. This is supported by our finding that the lowest median serum TARC/CCL17 level was observed at week 8, while lowest median EASI score was observed at week 12. Similar results were reported in the previous study of Guttman-Yassky et al,[10] investigating 54 moderate-to-severe AD patients treated with dupilumab for 16 weeks, where the mean percentage change

from baseline in serum TARC levels was the highest at week 4. In future, the change in p-EASI during the first weeks of treatment might potentially be used to predict response to dupilumab in AD patients.

The current study demonstrates that a biomarker signature (p-EASI) consisting of serum biomarkers TARC, IL-22, and sIL-2R adequately predicts disease severity in AD patients treated with dupilumab, in addition to previously published cohorts of TCS and CsA treated AD patients.[3,6] The use of p-EASI measured via a standardized assay will help to improve comparability of study outcomes in future clinical trials on new more targeted therapies for AD, but may also be helpful as an objective measure for treatment effects in daily practice.

CONFLICTS OF INTEREST

Dr Bakker reports personal fees from Sanofi Genzyme, outside the submitted work. Dr Hijnen reports grants and personal fees from AbbVie, personal fees from Eli Lilly, personal fees from Incyte, personal fees from Sanofi/Genzyme, grants from Thermo Fisher and personal fees from Pfizer, outside the submitted work. Dr de Bruin-Weller reports grants as Advisory Board Member/consultant AbbVie, grants as Advisory Board Member/consultant Pfizer, grants as Advisory Board Member/consultant Sanofi Genzyme, grants as Advisory Board Member UCB, grants as Advisory Board Member/consultant Eli Lilly, grants as Advisory Board Member/consultant Regeneron, grants as Advisory Board Member Galderma, grants as PI multicenter studies AbbVie, grants as PI multicenter studies Pfizer, grants as PI multicenter studies Galderma, outside the submitted work. Dr Thijs reports personal fees from Sanofi Genzyme, outside the submitted work. All other authors have nothing to disclose.

Daphne S. Bakker[1,2]
Lieneke F. M. Ariens[1]
Barbara Giovannone[2]
DirkJan Hijnen[3]
Eveline M. Delemarre[2,4]
Edward Knol[2]
Stefan Nierkens[2,4]
Marjolein S. de Bruin-Weller[1]
Judith L. Thijs[1,2]
Julia Drylewicz[2]

[1]*Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands*
[2]*Center for Translational Immunology, Utrecht, The Netherlands*
[3]*Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands*
[4]*Platform Immune Monitoring (PIM), University Medical Center Utrecht, Utrecht, The Netherlands*

Correspondence
Julia Drylewicz, Center for Translational Immunology, University Medical Center Utrecht, KC 02.085.2 P.O. Box 85090, 3508 AB Utrecht, The Netherlands.
Email: J.Drylewicz@umcutrecht.nl

ORCID

Daphne S. Bakker https://orcid.org/0000-0002-0193-5794
Lieneke F. M. Ariens https://orcid.org/0000-0001-5256-0091
DirkJan Hijnen https://orcid.org/0000-0003-3379-3425
Marjolein S. de Bruin-Weller https://orcid.org/0000-0002-1249-6993
Judith L. Thijs https://orcid.org/0000-0003-2753-5235
Julia Drylewicz https://orcid.org/0000-0002-9434-8459

REFERENCES

1. Flohr C. Atopic dermatitis diagnostic criteria and outcome measures for clinical trials: still a mess. *J Invest Dermatol*. 2011;131(3):557-559.
2. Thijs J, Krastev T, Weidinger S, et al. Biomarkers for atopic dermatitis: a systematic review and meta-analysis. *Curr Opin Allergy Clin Immunol*. 2015;15(5):453-460.
3. Thijs JL, Drylewicz J, Fiechter R, 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(6):1703-1705.
4. Walker C, Kagi MK, Ingold P, et al. Atopic dermatitis: correlation of peripheral blood T cell activation, eosinophilia and serum factors with clinical severity. *Clin Exp Allergy*. 1993;23(2):145-153.
5. Nograles KE, Zaba LC, Guttman-Yassky E, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol*. 2008;159(5):1092-1102.
6. Thijs JL, Drylewicz J, Bruijnzeel-Koomen C, et al. EASI p-EASI: predicting disease severity in atopic dermatitis patients treated with cyclosporin A. *Allergy*. 2019;74(3):613-617.
7. Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: end of the drought? *J Allergy Clin Immunol*. 2017;140(3):633-643.
8. Ariens LF, van der Schaft J, Bakker DS, et al. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: first clinical and biomarker results from the BioDay registry. *Allergy* 2019;75(1):116-126.
9. Furue M, Sugiyama H, Tsukamoto K, Ohtake N, Tamaki K. Serum soluble IL-2 receptor (sIL-2R) and eosinophil cationic protein (ECP) levels in atopic dermatitis. *J Dermatol Sci*. 1994;7(2):89-95.
10. Guttman-Yassky E, Bissonnette R, Ungar B, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;143(1):155-172.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.