

Clinical and molecular response to dupilumab treatment in pediatric atopic dermatitis: results of the German TREATkids registry [Letter]

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CONFLICT OF INTEREST STATEMENT

All authors declare no potential, perceived or real conflict of interest regarding the content of this manuscript.

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DATA AVAILABILITY STATEMENT

Data are not available.

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Clinical and molecular response to dupilumab treatment in pediatric atopic dermatitis: Results of the German TREATkids registry

To the Editor,

Dupilumab is a first-in-class biologic for moderate-to-severe atopic dermatitis (AD). Whereas multiple real-world studies confirmed its robust effectiveness and favorable safety in adults,¹ routine data on

children and adolescents are still scarce. In an interim analysis on 61 pediatric patients of the Dutch BioDay registry dupilumab significantly improved disease severity, however, results were difficult to interpret, because a considerable proportion of patients were

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in the wash-out or concomitantly treated with immunosuppressants at baseline.² TREATkids is a section of the TREATGermany registry and has been approved by the Medical Faculty of the Technical University of Dresden (No. EK 118032016) and by the respective ethics committees of the participating sites. It currently (data release May 2023) comprises 314 pediatric patients with moderate-to-severe AD (51.0% female, mean age 7.8). Their mean (\pm SD) baseline scores were Investigator Global Assessment [IGA, 3.2 (1.0)], Eczema Area and Severity Index [EASI, 13.4 (9.9)], peak pruritus numerical rating scale [PP-NRS, 5.5 (2.9)], and (Children's) Dermatology Life Quality Index [(c) DLQI, 9.5 (6.3)].

Systemic therapy was initiated in 99 of these 314 pediatric patients; most of them ($n=87$) received dupilumab. Fifty nine of those had at least one documented follow-up visit after 3 (± 14 days) or 6 months (± 28 days). Baseline mean EASI, PP-NRS and (C)DLQI scores were 18.1 (± 9.5), 7.1 (± 2.5) and 13.0 (± 5.7).

Overall, dupilumab treatment led to significant reductions of all severity scores (Figure S1). The proportion of patients with an EASI50, 75 and 90 response were 92.2%, 58.8% and 25.5% at month 3, and 91.4%, 62.9%, and 48.6% at month 6, that is, slightly higher than observed in trials.³ An EASI ≤ 7 reflecting mild disease was achieved by 78.4% and 82.9% at month 3 and 6. PP-NRS was reduced by 55.3% and 57.6% until month 3 and 6 ($p=2.72e-06$, $p=7.52e-05$), and mean (C)DLQI improved by 59.7% and 62.3% ($p=7.41e-08$). At month 3, 84.4% had experienced a 4-point reduction of the (C)DLQI (Table 1). Dupilumab was well tolerated with adverse events reported in only four patients. Three children experienced conjunctivitis and one

child developed blepharitis, which led to discontinuation. Facial eczema was reported in one patient.

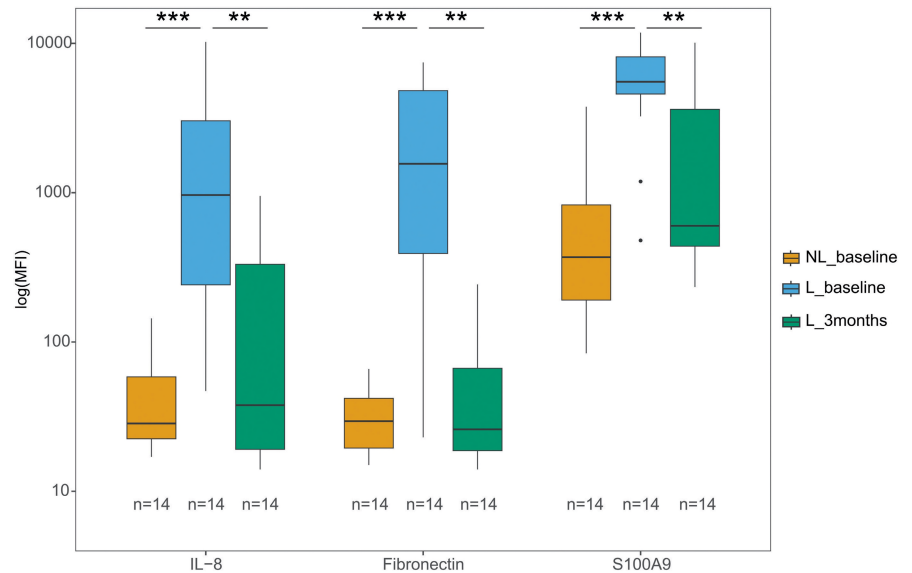
A sensitivity analysis on patients with data on both month 3 and 6 indicated that while baseline characteristics did not differ significantly between children ($n=14$) and adolescents ($n=14$), the latter showed slightly more pronounced improvements with a median EASI reduction at month 3 of 88.2% versus 77.5%, and EASI75 response rates of 78.6% versus 57.1% (Table S1). We additionally analyzed 21 AD candidate biomarkers in tape strips from 14 patients using a Luminex assay (Bio-technie, Minneapolis, USA). Fifteen markers moderately correlated with disease severity measured by the EASI (Table S2). Eighteen proteins showed differential expression in lesional versus non-lesional skin at baseline. At month 3, 15 of these had decreased significantly (Table S3) and no longer showed significant differences to non-lesional skin. In the absence of data on healthy individuals, it is unclear whether they reached levels of non-AD skin. The most pronounced reductions were observed for fibronectin ($\log_2FC=4.63$), IL-8 ($\log_2FC=3.52$), and S100A9 ($\log_2FC=2.13$) (Figure 1). Fibronectin is central for adhesion and internalization of *S. aureus*.⁴ IL-8 has pleiotropic effects, including attraction and activation of neutrophils, which contribute to *S. aureus* colonization by release of neutrophil extracellular traps.⁵ S100A9 was reported to correlate with AD severity.⁶

The results from our analysis demonstrate that dupilumab treatment is safe and leads to clinical and molecular improvements in the majority of pediatric AD patients. Larger-size and longer-term routine data along with analysis of extended biomarker panels will be

	Baseline	Month 3		Month 6	
			<i>p</i> value		<i>p</i> value
Severity scores, mean (\pm SD)					
EASI	18.3 \pm 9.8	4.5 \pm 4.0	7.5495e-15	4.1 \pm 4.7	4.7468e-10
oSCORAD	44.3 \pm 11.0	21.1 \pm 11.0	3.7303e-14	18.1 \pm 11.3	2.4145e-10
IGA	3.6 \pm 0.8	2.0 \pm 0.9	2.7204e-11	1.8 \pm 1.0	6.4748e-07
PGA	3.9 \pm 0.8	2.2 \pm 1.0	6.3848e-11	2.1 \pm 1.0	1.4483e-06
POEM	20.0 \pm 5.5	8.5 \pm 6.5	2.7480e-11	8.9 \pm 5.7	2.1118e-08
(C)DLQI	12.9 \pm 5.7	5.2 \pm 4.8	7.9429e-10	4.3 \pm 4.7	8.9659e-08
Peak itch	7.2 \pm 2.4	3.2 \pm 2.5	2.5421e-06	2.9 \pm 2.4	1.6520e-04
Predefined endpoints, %					
EASI50 %		92.0%		90.9%	
EASI75 %		58.0%		60.6%	
EASI90 %		26.0%		45.5%	
EASI ≤ 7	7.0%	78.0%		81.8%	
IGA ≤ 1	0.0%	29.4%		42.4%	
PGA ≤ 1	0.0%	25.5%		27.3%	
4-point reduction peak itch		63.6%		75.9%	
4-point reduction (C) DLQI		84.4%		80.0%	

TABLE 1 Severity scores and predefined endpoints over time.

FIGURE 1 Treatment with dupilumab reduces levels of AD-associated stratum corneum biomarkers. Changes of protein marker levels (values in median fluorescence intensity (MFI)) in stratum corneum samples of non-lesional skin at baseline and lesional skin at baseline and 3 months after dupilumab treatment. Comparisons between time points were made using the Wilcoxon signed-rank test. $**p < 0.01$, $***p < 0.001$, (Benjamini-Hochberg corrected).



key to more comprehensively evaluate effects of systemic therapies in pediatric AD.

AUTHOR CONTRIBUTIONS

Dora Stölzl and Stephan Weidinger designed the study; Inken Harder and Melina Fonfara performed biomarker measurements; Dora Stölzl, Nicole Sander and Doreen Siegels contributed to methodology and analyzed and visualized the data; Jochen Schmitt, Thomas Werfel and Stephan Weidinger supervised the analysis; Dora Stölzl, Nicole Sanders and Stephan Weidinger wrote the manuscript draft; all authors reviewed and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

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Inc., Janssen-Cilag, Johnson & Johnson, Klinge Pharma, Kymab, Leo Pharma, Medac, MSD, Neubourg Skin Care GmbH, Novartis, Pfizer, Principia Biopharma, Regeneron, Sandoz, Sanofi, UCB Pharma. Katja Nemat has received lecture and/or consultancy fees from Sanofi, Stallergenes, Berlin-Chemie and HAL. Susanne Lau has received grants from Novartis, DBV, Infectopharm and honoraria from ALK, Allergopharma, Boehringer, GSK, LEO Pharma, Nutricia, Lilly, Viatrix, GSK, and Sanofi-Aventis. Annice Heratizadeh reports personal fees from AbbVie, Almirall, ALK, LEO Pharma, Novartis, Pierre Fabre, Klinge Pharma, Sanofi, Beiersdorf, Hans Karrer, Nutricia, Meda, and Lilly; and grants from Janssen and Pfizer. Andreas Wollenberg has received institutional research grants, consulting fees and/or study support from Abbvie, Aileens, Almirall, Beiersdorf, Galapagos, Galderma, Glenmark, GSK, Janssen, LEO Pharma, Eli Lilly, L'Oreal, MedImmune, MSD, Novartis, Pfizer, Pierre Fabre, Regeneron, Sanofi and UCB. Jochen Schmitt reports institutional grants for investigator-initiated research from the German Federal Joint Committee, German Ministry of Health, German Ministry of Research, European Union, German Federal State of Saxony, Novartis, Sanofi, ALK, and Pfizer. He participated in advisory board meetings as a paid consultant for Sanofi, Lilly, and ALK. Prof. Schmitt serves the German Ministry of Health as a member of the German National Council for Health and Care. Thomas Werfel has received institutional grants from LEO Pharma and Novartis, has performed consultancies for Abbvie, Almirall, Janssen, Galderma, LEO, Lilly, Novartis, Pfizer and Sanofi-Regeneron and has lectured at events sponsored by Abbvie, Janssen, Celgene, Galderma, LEO Pharma, Lilly, Sanofi and Novartis. Stephan Weidinger has received institutional research grants from LEO, Pfizer and Sanofi; has been an advisor and/or received speakers' honoraria from AbbVie, Almirall, Boehringer, Eli Lilly, Galderma, LEO Pharma, Pfizer, Sanofi, and Regeneron; has participated in clinical trials of AbbVie, Almirall, Anaptys Bio, Boehringer-Ingelheim, Eli Lilly, Galderma, GSK, Incyte Inc., Janssen-Cilag, Kymab, Leo Pharma, Pfizer, Regeneron, Sanofi, UCB. All of the other authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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