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RESPONSE TO LETTER

Response to Comments on The Association of Inflammatory Indexes Derived From Peripheral Blood Cell Count and Clinical Signs with Response to Treatment with Dupilumab in Pediatric Patients with Moderate-to-Severe Atopic Dermatitis [Response to Letter]

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Dear Editor

Thank you for your thoughtful critique of our study. We appreciate your engagement with our work and the opportunity to address your concerns. Below, we respond to each of your points.

Retrospective Design and Confounding Variables

You raised concerns about the retrospective design and potential confounding variables such as environmental exposures, comorbidities, and concurrent medications. While retrospective studies inherently carry limitations in controlling for confounders, we implemented several strategies to mitigate bias:

Structured Data Collection

We systematically recorded comorbidities, concurrent medications (eg, topical corticosteroids, antihistamines), and environmental exposures (eg, allergen sensitization status) in our original cohort. Based on the literature, we selected factors such as age, gender, disease duration, and IgE levels, which may influence the response to dupilumab, and these variables were included in our multivariate logistic regression model to adjust for their potential influence.

Homogeneity of the Cohort

All patients met stringent inclusion criteria (Hanifin and Rajka criteria for AD diagnosis and standardized dupilumab dosing), reducing heterogeneity.

While prospective studies are ideal, retrospective analyses remain critical for generating real-world evidence in pediatric populations, particularly in younger age groups (<6 years) underrepresented in clinical trials. Future studies will incorporate propensity score matching to further address confounding.

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Single-Center Design and Selection Bias

You highlighted potential selection bias due to the single-center design. However, our center serves a diverse population across urban and rural regions of Southwest China, with a broad spectrum of AD severity (EASI 6–60 at baseline). Notably, 81.7% of our cohort were children <6 years, a population rarely studied in prior trials. While multi-center collaborations are valuable, our findings align with Phase III trials in younger children (eg, Paller et al, 2022[1]), supporting their validity. We are currently collaborating with three tertiary hospitals in China to validate these findings in a multi-center cohort.

Reliance on Peripheral Blood Cell Counts

You questioned whether blood cell-derived indices fully capture AD's inflammatory complexity. While cytokines (eg, IL-31, TARC) and skin biomarkers (eg, filaggrin) provide mechanistic insights, their clinical utility is limited by cost, invasiveness, and lack of standardization. In contrast, blood cell ratios (eg, ELR, NLR) are inexpensive, reproducible, and routinely available, making them pragmatic tools for real-world practice. Our findings align with recent studies, showing the predictive value of ELR in adults with AD treated with upadacitinib (Hagino et al, 2023[2]). Future work will integrate cytokine profiling (eg, IL-4/IL-13 levels) to explore synergies with blood cell indices.

Short Follow-Up Duration

The 16-week follow-up was chosen to align with pivotal phase III trials (eg, Paller et al, 2022[1]) and regulatory guidelines for assessing dupilumab's early efficacy. While longer-term data are needed, our study demonstrates that the change of ELR was positively correlated with the change of EASI score during dupilumab treatment, and baseline ELR strongly correlates with EASI75 achievement (AUC = 0.654) at 16 weeks, a critical milestone in AD management. We are conducting a 52-week extension study to evaluate ELR's utility in predicting sustained remission.

Lack of Subgroup Analysis by Disease Severity/Phenotype

AD's heterogeneity is well recognized. Although our cohort focused on moderate-to-severe AD, we stratified patients by age (<6 vs ≥6 years) and observed distinct ELR dynamics: younger children showed a continuous ELR decline, whereas older children exhibited an initial transient rise. This aligns with Weissmann et al (2024[3]), who reported an age-dependent change in neutrophilic vs eosinophilic inflammation. Future studies will phenotype patients by IgE status and filaggrin mutations to refine predictive models.

Genetic Factors

You emphasized the role of genetic factors, such as filaggrin (FLG) mutations. While *FLG* mutations are linked to AD severity, recent evidence suggests no significant difference in dupilumab response between *FLG* mutant and wild-type patients (Clabbers et al, 2024[4]). This supports our focus on ELR as a biomarker independent of genetic background. Nonetheless, we acknowledge the need to explore interactions between genetic variants and inflammatory indices in larger cohorts.

Conclusion

We agree that prospective, multi-center studies integrating cytokines, genetic data, and long-term follow-up are essential to advance personalized AD care. However, our study provides novel insights into ELR's role as a practical, cost-effective biomarker for predicting dupilumab response in children <6 years—a population with urgent unmet needs. We thank you for your constructive feedback and welcome collaboration to address these questions in the future work.

Disclosure

The authors report no conflicts of interest in this communication.

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