RESEARCH LETTER

Serum IL-13 and IL-31 Levels are not Attenuated upon Dupilumab Treatment: Lessons from a Prospective Cohort

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Submitted Nov 1, 2025. Accepted after revision Nov 6, 2025
Published Jan 14, 2026. DOI: 10.2340/actadv.v106.adv-2025-0147 Acta Derm Venereol 2026; 106: adv-2025-0147.

To the Editor,

Dupilumab, a monoclonal antibody targeting interleukin (IL)-4 and IL-13 signalling, has demonstrated clinical efficacy in moderate-to-severe atopic dermatitis (AD). This prospective cohort study evaluated serum Th2 cytokines (IL-4, IL-13, IL-31) before and after dupilumab. Eleven patients with severe AD and 12 healthy controls were enrolled. Cytokine levels were measured by enzyme-linked immunosorbent assay before and 12–16 weeks after initiation of dupilumab. Baseline IL-13 levels were significantly elevated in AD patients compared to controls ($p<0.0001$), while IL-31 levels did not differ ($p=0.17$); IL-4 was consistently undetectable. No significant changes in IL-13 or IL-31 levels were observed following treatment ($p=0.99$ and $p=0.44$, respectively), including among responders. Due to the small cohort and high response rate, correlation between baseline cytokines and clinical response was limited. Findings suggest that serum IL-13 and IL-31 are not attenuated upon dupilumab and thus are not reliable predictors of dupilumab response. These results underscore the predominance of localized cutaneous immune dysregulation in AD and highlight the need for improved systemic biomarkers to guide personalized therapy.

Atopic dermatitis (AD) is a chronic type 2 skin disorder that significantly affects patients' quality of life. Dupilumab, a human monoclonal antibody targeting interleukin (IL)-4 and IL-13, has been introduced as a systemic treatment choice (1).

Clinical trials and real-life data revealed that adults with moderate-to-severe AD who receive biweekly dupilumab injections show marked improvement across various clinical and patient-reported outcomes such as the Eczema Area Severity Index score, the Dermatology Life Quality Index, and itch Numeric Rating Scale scores (2).

Analyses of biomarkers reveal that dupilumab significantly modulates Th2-associated tissue markers and the molecular signature of AD (2). However, no serum markers have been consistently associated with predicting response to dupilumab. As Janus kinase inhibitors serve as an alternative therapeutic choice, such serum markers may potentially predict response, allowing for a more personalized approach to patient care.

The study is a prospective cohort study, performed at the Department of Dermatology at Rambam Health Care Campus, Haifa, Israel. We hypothesized that the serum levels of Th2 cytokines would be attenuated upon treatment among responders and aimed to study cytokine levels in AD patients and healthy controls, as well as before and after dupilumab treatment. We calculated sample size according to the formula $n=([(Z\alpha/2+Z\beta]^2 \cdot 2 \cdot \sigma^2)/\Delta^2$. Alpha ($\alpha$)=1.96, beta ($\beta$)=0.84 and σ was calculated as 10% of the mean of control values (20 for IL-13, and 200 for IL-31). Delta (Δ) was calculated as 30% of the mean of control values (50 for IL-13, and 500 for IL-31). The calculated sample size was 2.5, i.e. at least 3 patients were needed for each group.

Continuous variables included age, serum IgE and cytokine levels. Categorical variables included Investigator Global Assessment (IGA) scores and type of treatment. Descriptive statistics were presented as means and standard deviations or medians and interquartile ranges. Group comparisons were performed using *t*-tests or non-parametric tests when appropriate.

During 2020, we enrolled 11 patients diagnosed with severe AD who started treatment with dupilumab after the failure of earlier lines of systemic therapy, and 12 healthy controls. Blood samples were collected from each patient before the initiation of dupilumab. Additionally, we had 5 follow-up samples taken after 12–16 weeks of treatment. IGA was recorded before and 12–16 weeks after dupilumab (**Table I**). No patient was lost to follow-up during this period.

Serum samples were assessed for IL-13, IL-4 and IL-31 levels using enzyme-linked immunosorbent assay (ELISA) technique. The ELISA kit used for the

Table I. Clinical characteristics and serum IgE levels

Patient	IGA before treatment	IGA after treatment	IgE level (IU) (normal<115 IU)
1(M,84)	4	0	310
2(M,78)	4	1	733
3(M,23)	4	1	5,070
4(F,36)	4	3	441
5(F,30)	3	0	5,000
6(F,26)	3	1	232
7(F,38)	3	1	6,000
8(F,35)	3	1	106
9(M,28)	3	1	6,830
10(M,48)	3	1	21,500
11(F,26)	3	4	19,500

IGA:Investigator Global Assessment.

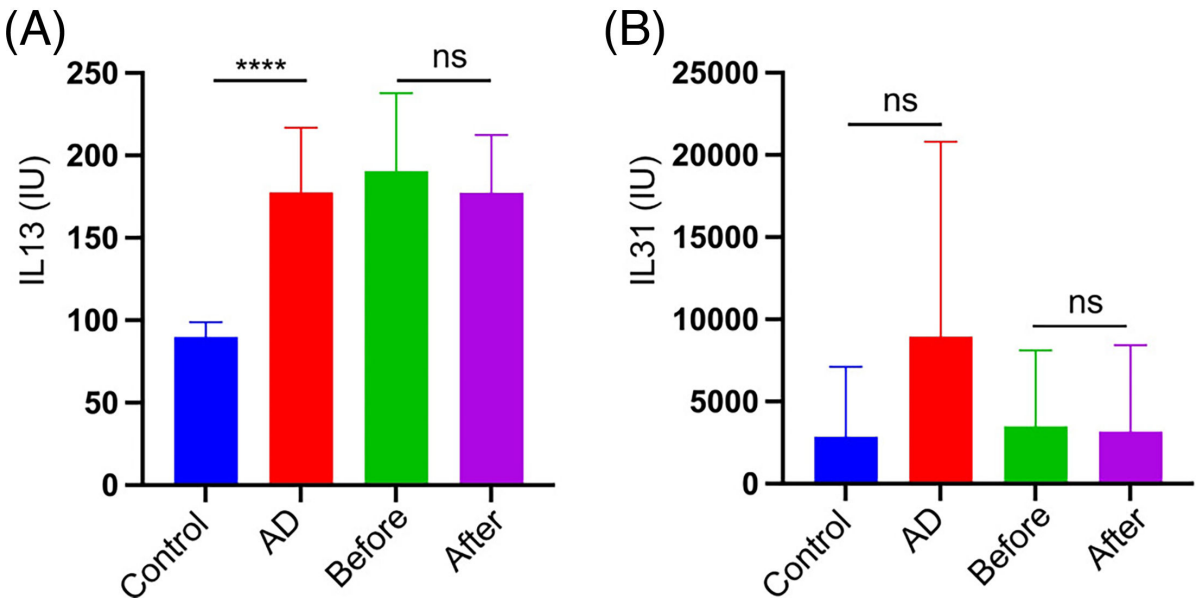

Fig. 1. (A) Serum IL-13 levels in healthy controls (control), AD patients (AD), and 5 AD patients with 2 consecutive samples before (before) and after 3 months of dupilumab (after). (B) Serum IL-31 levels in healthy controls (control), AD patients (AD), and 5 AD patients with 2 consecutive samples before (before) and after 3 months of dupilumab (after).

quantification of cytokine levels was obtained from R&D Systems (Catalog No. DY2824 for IL-31, D1300B for IL-13, D4050 for IL-4).

Serum levels of IL-13 were higher in AD patients than in controls [180.51±39.76 (130.5–252.9) vs 89.9±8.8 (77.7–103.1), respectively, $p<0.0001$, **Fig. 1**A]. Conversely, the levels of IL-31 were similar to controls [6,931.5±10,013 (0–32,809) vs 2,870±4,235 (0–12,656), $p=0.17$, Fig. 1B] In addition, we did not reveal any difference between the serum levels of the biomarkers IL-13 [190.5±47.3 (130.5–152) vs 177.4±35.1 (147.2–223.9), $p=0.99$], or IL-31 [3,496±4,619 (656.4–1,143) vs 3,175±5,257 (84.9–12,414), $p=0.44$] before and after dupilumab (Fig. 1A, B). IgE levels ranged from 116 IU to 19,500 IU (normal <115 IU). Notably, serum IL-4 levels were consistently extremely low or undetectable, even in patients with severe AD. Out of 11 patients with AD, 2 patients were considered non-responders at weeks 12–16 (Table I). In this cohort, evaluating the correlation between the level of IL-13/IL-31 before dupilumab treatment and response was limited because of the small number of participants and the high response rates. However, the lack of a meaningful change in cytokine levels upon dupilumab treatment suggests that IL-13/IL-31 serum levels cannot reliably predict response.

Previous studies have shown that the AD skin proteome exhibits upregulation of inflammatory cytokines in lesional and non-lesional skin compared to controls (3). It was also demonstrated that skin cytokines were significantly upregulated compared to serum levels, suggesting that the cutaneous immune response is the central mechanism driving the amplification of the inflammatory cascade and cytokine production (3).

This work contributes to the available evidence by providing data on serum Th2 cytokines upon treatment, showing that dupilumab does not attenuate serum IL-13 and IL-31 levels. Given the emergence of novel biological treatments for AD and the need for guidance in clinical practice, this work underscores the need for a better assessment of serum biomarkers in predicting patient response to treatment.

ACKNOWLEDGEMENTS

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

IRB approval status: Reviewed and approved by Western IRB; approval 0459-19-RMB.

Conflict of interest: Dr. Avitan Hersh is a consultant and lecturer for Sanofi, Abbvie, Eli Lilly, Neopharm, Pfiser and Leo pharma.

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