

Letter to the Editor

Serum IL-17 levels in patients with allergic rhinitis

To the Editor:

Allergic rhinitis (AR) is characterized by an inflammatory reaction sustained by T_H2 polarization. This T_H bias is evidenced by the PBMCs of patients with AR, which display a predominant IL-4 production by T_H2 cells compared with IFN- γ expression by T_H1 cells. This functional dichotomy between T_H1 and T_H2 has been more recently modified by the discovery of another T-lymphocyte subset, namely T_H17 cells. In particular, the discovery of T_H17 cells has been fundamental to our understanding of how T_H1 cells can actually mediate inflammatory events by producing IFN- γ .¹

T_H17 cells are characterized by the production of various cytokines, including IL-17, IL-6, TNF- α , and IL-22. IL-17 is involved in tissue pathology in autoimmune models, and anti-IL-17 reduced joint inflammation and bone erosion in an experimental arthritis model.¹ Furthermore, anti-IL-17 reduced neutrophil infiltration in an experimental murine asthma model² and increased eosinophil infiltration, whereas IL-17 induced recruitment and was identified as a survival factor for airway macrophages.³ These facts seem to suggest a regulatory role for IL-17.⁴ However, the role of T_H17 cells in allergic inflammation is still obscure. Experimental studies seem to suggest that T_H17 cells might be involved in the process of neutrophil infiltration that occurs during the acute phase of the allergic reaction.¹ One study exploring the role of IL-17 in patients with allergic or viral rhinitis showed increased concentrations of IL-17 in nasal secretions only in the latter group.⁵

The assessment of a cytokine at the serum level would certainly simplify clinical evaluation. Previous studies have shown that IL-17 serum levels are increased in several disorders: acute hepatic injury,⁶ rheumatoid arthritis,⁷ and McArdle disease.⁸ However, a very recent study failed to demonstrate increased IL-17 serum levels in allergic asthmatic subjects.⁹ Therefore the aim of the present study was to evaluate whether there is an increase in IL-17 serum levels in patients with AR.

The study included 19 birch-monosensitized patients (11 male and 8 female patients; mean age, 42.1 years) with a history of moderate-to-severe persistent AR and 8 healthy control subjects (4 male and 4 female subjects; mean age, 46.3 years). All subjects were healthy (except for AR) without any active disorder, including rhinosinusitis, and asthma was excluded in all patients with rhinitis. Skin prick tests, blood sampling for assessment of peripheral eosinophil counts and serum IgE and IL-17 levels, and allergen-specific conjunctival challenges were performed in all patients. The study was conducted during the winter, outside the pollen season, when all patients were symptom free. The study was approved by the local ethics committee and performed with the written informed consent of all participants. AR was diagnosed according to validated criteria.¹⁰

Skin prick tests were performed according to the guidelines of the European Academy of Allergy and Clinical Immunology.¹¹ Total and specific IgE levels were measured by using the Fluorezyme immunoassay (calibrator range, 2-5000 and 0-100 kU/L, respectively; Phadia, Uppsala, Sweden), allergen-specific conjunctival challenges were performed according to validated

criteria,⁵ and the allergen threshold dose was determined for each patient. The test was performed after blood drawing.

The human IL-17 immunoassay (Quantikine IL-17 Immunoassay; R&D Systems, Inc, Milan, Italy) measures IL-17A and uses the quantitative sandwich enzyme immunoassay technique. It was performed according to the manufacturer's instructions, and results were expressed as picograms per milliliter. The range of IL-17 detectable in the ELISA was 0.28 to 5.47 pg/mL in healthy subjects and 1.81 to 141.29 pg/mL in allergic subjects.

Descriptive statistics were first performed, and quantitative parameters were reported as the median and number of subjects (allergic and healthy) with detectable serum IL-17 (including values <15 pg/mL). The nonparametric Wilcoxon test and Pearson test were used to compare samples and to study correlation, respectively. The package S-Plus (MathSoft Corp, Needham, Mass) was used for all analyses.

Allergic patients exclusively sensitized to birch alone presented significantly higher median levels of IL-17 (median, 25.63 pg/mL; minimum, 1.81 pg/mL; maximum, 141.29 pg/mL) compared with healthy control subjects (median, 1.33 pg/mL; minimum, 0.28 pg/mL; maximum, 5.47 pg/mL; $P = .018$; see Fig E1 in this article's Online Repository at www.jacionline.org). Moreover, IL-17 was evidenced in a higher percentage of allergic patients than in healthy individuals (7/19 vs 1/8); therefore 7 allergic patients and 1 healthy subject were defined as IL-17⁺.

The subanalysis between IL-17-producing (IL-17⁺) and non-IL-17-nonproducing (IL-17⁻) allergic patients showed that IL-17⁺ patients had significantly higher serum total IgE levels (IL-17⁺ patients: median, 402 kU/L; minimum, 350 kU/L; maximum, 722 kU/L; IL-17⁻ patients: median, 134 kU/L; minimum, 10 kU/L; maximum, 280 kU/L; $P = .0001$), specific IgE levels to birch (IL-17⁺ patients: median, 84.3 kU/L; minimum, 71.3 kU/L; maximum, 101 kU/L; IL-17⁻ patients: median, 16.75 kU/L; minimum, 4.13 kU/L; maximum, 65 kU/L; $P = .0004$), lower allergen threshold dose (IL-17⁺ patients: median, 25 biologic unit [BU]; minimum, 12.5 BU; maximum, 25 BU; IL-17⁻ patients: median, 50 BU; minimum, 50 BU; maximum, 100 BU; $P = .0002$), and a trend toward higher eosinophil counts (IL-17⁺ patients: median, 5.2/mm³; minimum, 4.1/mm³; maximum, 8/mm³; IL-17⁻ patients: median, 3.95/mm³; minimum, 0.2/mm³; maximum, 7.7/mm³; $P = .07$; see Fig E2 in this article's Online Repository at www.jacionline.org). No significant correlation was found between IL-17⁺ patients and specific IgE levels, eosinophil counts, and allergen threshold doses. A negative correlation trend, even if not statistically significant ($r = -0.7$, $P = .06$), was found between IL-17⁺ patients and total IgE levels.

These data show that the patients with the most severe birch allergy, evaluated during a period without exposure to the causal pollen, have measurable serum IL-17 levels. However, the present study is in conflict with previous studies,^{5,9} likely because the patient populations were different, as was the period of observation. Klemens et al⁵ showed that only patients with viral rhinitis had increased IL-17 levels in nasal secretions. These contradicting results might be justified by both the different site of evaluation and patient characteristics. Lei et al⁹ reported that IL-17 serum levels in asthmatic patients are similar to those in healthy control subjects, and in this study the contrasting results might be explained by the different clinical characteristics of the patients,

mainly concerning the type of sensitization. Moreover, neither study considered the atopic status of patients, such as IgE level, eosinophil count, and allergy degree assessed by means of allergen challenge. Therefore the careful assessment of patients could allow us to detect IL-17 producers. Indeed, the present study evaluated a very select group of patients who were monosensitized to birch. Birch allergy in Ligurian patients has been characterized by a relevantly increased prevalence and severity of symptoms.¹² Of interest, patients with the highest degree of birch allergy were IL-17 producers. This finding is particularly relevant considering that the period of observation was outside the pollen season. This phenomenon is not a complete surprise, however, because it might be dependent on a chronic allergic reaction to birch in hypersensitized patients. In this scenario T_H17 cells are implicated in chronic events of allergic reaction that endure over time.¹³ In fact, independent of allergen exposure, IgE production is typically continuous and persistent. Thus IL-17 measurement might define severe immune response, such as that seen in IL-17⁺ allergic patients, confirming a previous study that proposed high IL-17 serum levels as a new marker of severity of acute hepatic injury.⁶

On the other hand, this study has some limitations. First, we evaluated a limited number of patients (it is very difficult to enroll monosensitized patients). Second, patients were evaluated only outside the pollen season because all were successively treated with specific immunotherapy. Therefore further studies are required to confirm these preliminary data, mainly concerning the evaluation of patients during the pollen season.

In conclusion, this study provides the first evidence that serum IL-17 levels might be increased in patients monosensitized to birch with the most severe AR. Thus increased IL-17 serum levels can be considered a marker of severe allergy.

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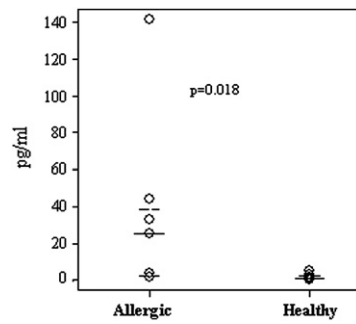


FIG E1. Serum IL-17 distribution in allergic patients and healthy subjects. Single values are represented together with medians (*solid lines*) and interquartile ranges (*dotted lines*).

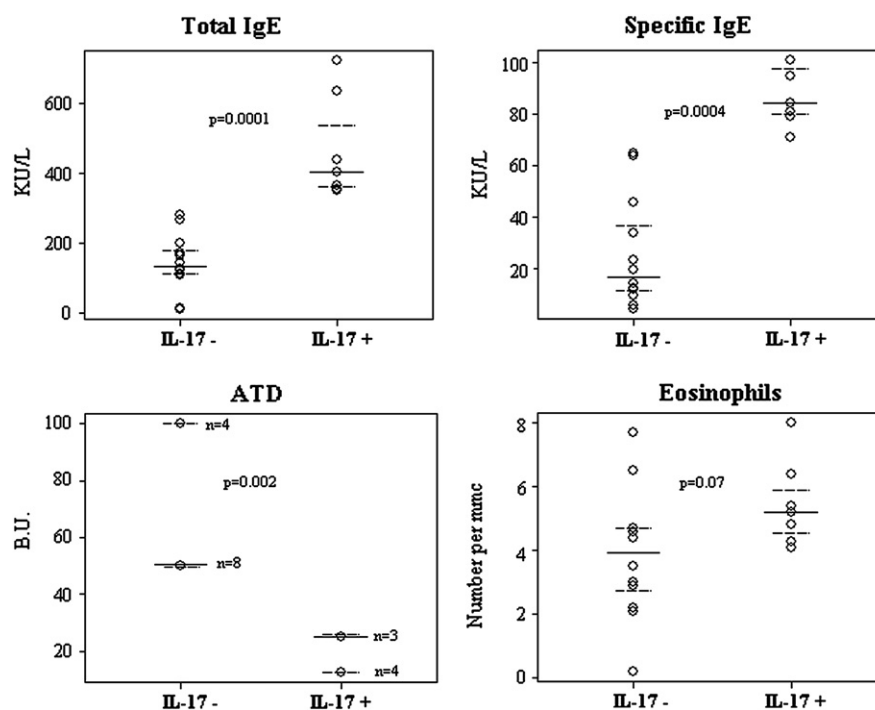


FIG E2. Serum total IgE levels, serum specific IgE levels to birch, allergen threshold dose (ATD) at allergen-specific conjunctival challenge, and peripheral eosinophils in IL-17⁺ and IL-17⁻ patients. Single values are represented together with medians (solid lines) and interquartile ranges (dotted lines). Because allergen threshold doses are concentrated around 4 values, the number of patients under each point is reported.