

IgE levels are negatively correlated with clinical response to ciclosporin in chronic spontaneous urticaria

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Dear Editor, First- and second-line treatment of chronic spontaneous urticaria (CSU) includes second-generation H1 antihistamines. However, treatment shows little benefit in > 50% of cases.^{1,2} Omalizumab and ciclosporin are recommended as third- and fourth-line treatments, respectively.¹ Despite its inferior safety profile to omalizumab,^{1,2} the efficacy of ciclosporin has been shown in controlled trials and case series, with a good response seen in approximately 60% of patients with severe CSU.³

Biomarkers predicting treatment response in CSU have been investigated in several studies. Elevated plasma D-dimer and positive basophil histamine release assay predict better clinical response to ciclosporin.⁴ Recent retrospective studies have reported that response to omalizumab is linked to high serum IgE.^{5,6} However, no studies have addressed the influence of serum IgE in other CSU therapies.

With the objective of evaluating whether IgE levels influence treatment response to ciclosporin, we performed a retrospective study between 2015 and 2017 at the Department of Dermatology, Coimbra University Hospital, analysing 34 adult patients with CSU treated with 3 mg kg⁻¹ daily ciclosporin for a minimum of 3 months. While awaiting approval from institutional authorities to use omalizumab, ciclosporin was used in all consecutive patients with moderate-to-severe CSU refractory to more than two H1 antihistamines in a fourfold dose, provided there was no known contraindication to use the drug. In good responders, omalizumab was stopped.

We analysed demographic data, treatment duration, atopic status, baseline total IgE levels (normal ≤ 100 IU mL⁻¹), C-reactive protein (CRP; normal ≤ 0.50 mg dL⁻¹), and antinuclear antibody (ANA; normal titre level $\leq 1 : 80$) or antithyroid antibody (ATA), evaluated by indirect immunofluorescence and chemiluminescent immunoassay, respectively. Clinical response was evaluated using Urticaria Activity Score Over 7 Days (UAS7) before and at month 1, 2 and 3 of treatment. A good clinical response was considered to be UAS7 ≤ 6 at month 3. Blood pressure and glomerular filtration rate were controlled at similar intervals. A χ^2 test and a Mann–Whitney U-test were used to compare categorical and nonparametric data, respectively. Spearman's rank correlation coefficient and logistic

regression were also applied. A P-value < 0.05 was considered to be statistically significant.

Women represented 88% of all patients, mean patient age was 45.09 ± 13.86 years, median disease duration was 64 months (range 35–148) and 94% had angio-oedema. CRP was elevated in 71% (mean 1.24 ± 0.88 mg dL⁻¹) of patients, ANA was positive in 62% of patients and ATA in 18%. (Full details of characteristics of all patients studied are available on request.)

Treatment was considered successful in 18 patients (53%); 89% of these improved within the first month, consistent with previous studies.⁴ Considering all patients, a median UAS7 before treatment of 30 (range 27–35) decreased to 14 (range 3–24.25) and 4.5 (range 0–20) after 1 and 3 months, respectively. None of the responders relapsed during a 2-month follow-up after tapering ciclosporin. All nonresponders (93.8%) except one responded further to omalizumab. Adverse effects occurred in 26.5% of the patients, mostly mild hypertension, which was controlled with antihypertensive drugs (20.5%), and upper respiratory tract infections (12.5%), which did not require discontinuation of treatment. (Full efficacy and safety results of all patients studied are available on request.)

Mean serum IgE was significantly lower in ciclosporin responders (mean 43.00 IU mL⁻¹; range 17–70.25) vs. nonresponders [148.50 IU mL⁻¹; range 68.75–393.25 ($P = 0.001$)]. Moreover, serum baseline IgE showed a moderately significant negative correlation with the decrease in UAS7 at month 3 ($r_s = -0.514$, $P = 0.002$). When patients were divided into two subgroups based on the normal IgE cut-off (< 100 IU mL⁻¹), a normal IgE value was associated with a higher probability of response to ciclosporin, with an adjusted odds ratio of 33.9 [95% confidence interval 3.21–357.33; $P = 0.003$ (Fig. 1)]. There was a significant difference in clinical response between the sexes, with all men being nonresponders, although they constituted a small, nonrepresentative sample. No association was found between response to ciclosporin and ANA, ATA, CRP, patient age or duration of urticaria.⁷

This study revealed that low or normal IgE levels seem to identify a subgroup of patients with CSU with a higher probability of having a good response to ciclosporin and, according to other studies, a later and/or lower response to omalizumab.^{5,6} Individuals with a good response to immunosuppressive therapy may represent the subtype of type II autoimmune CSU (circulating IgG anti-IgE and/or anti-Fc ϵ RI on mast cells);⁸ patients with this subtype are mostly female

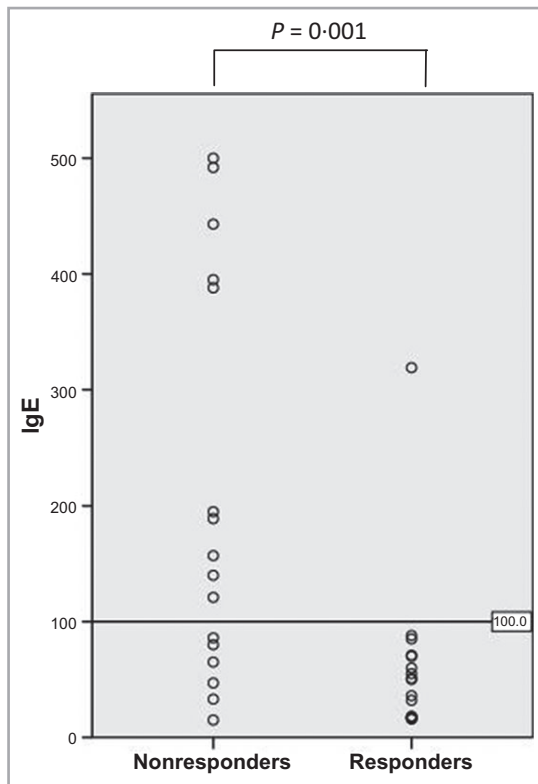


Fig 1. Clinical response to ciclosporin categorized by a serum baseline IgE cut-off of 100 IU mL⁻¹. There was a highly significant difference between the two subgroups ($P = 0.001$).

with positive serum basophil histamine release assay and lower basophil FcεRI expression.^{4,8} Interestingly, contrary to ciclosporin, best responders to omalizumab have higher IgE levels and are mostly male.^{5,6} These patients probably have IgE-recognizing autoantigens (type I autoimmune CSU),⁸ as omalizumab rapidly targets this free IgE, preventing its binding to mast cells and basophils and consequent degranulation.

The limitations of this study are its retrospective nature and the small number of patients.

These observations suggest that total IgE, which is easily assessed in clinical practice, can be a potential and relevant marker with which to predict clinical response to ciclosporin, as has previously been shown for omalizumab, but with an inverse correlation.

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