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Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab

To the Editor,

Anti-IgE treatment with omalizumab was shown to be effective in chronic spontaneous urticaria (CSU) in randomized controlled trials¹ and real-life studies.^{2,3} Omalizumab, the first licensed therapy for H₁-antihistamine refractory CSU, prevents IgE binding to its high-affinity receptor (FcεRI).⁴ As a result, free serum IgE levels decline and the expression of FcεRI receptors on basophils and mast cells is downregulated.⁴ Moreover, omalizumab appears to dissociate pre-bound IgE from mast cells and basophils.⁴

Nonresponders to omalizumab therapy remain ill-defined. Here, we compared complete responders (CR) to nonresponders (NR) and partial responders (PR) to identify predictors for response. In total, we analyzed 85 patients from four GA²LEN urticaria centers of reference and excellence (UCAREs),⁵ 43 CR, 23 PR, and 19 NR (Table 1). Complete, partial and nonresponses were defined as the reduction in signs and symptoms by ≥90%, by ≥30% but <90%, and by <30% (physicians global assessment), respectively, after 2–4-weekly injections of omalizumab 300 mg. All centers provided data on NRs comparing patient characteristics, laboratory values, and treatment response. In addition, all centers were asked to provide data on at least one randomly selected PR and CR per entered NR. Because different methods of total IgE assessment with different reference values were used in the different centers, the total IgE values were transferred to percentage scores of the respective upper reference value. Total IgE levels of 0%–10%, >10%–50%, and >50%–100% of the upper reference value were regarded as low normal, mid-normal, and high normal, whereas total IgE levels of >100%–250%, >250%–1000%, and >1000% of the upper reference value were regarded as slightly elevated, moderately elevated, and highly elevated. Statistical analyses were carried out with SPSS (IBM SPSS Statistics, Version 22, Armonk, NY, USA).

No differences were found between the three responder groups (CR, PR, and NR) with regard to age (ANOVA) and gender distribution (chi-squared test). In contrast, disease duration (Kruskal-Wallis test, $P < 0.05$) and categorized total IgE levels were significantly different (chi-squared test, $P < 0.05$), as were non-categorized total IgE percentage values (Kruskal-Wallis test, $P < 0.001$), determined before the initiation of omalizumab treatment. CR, PR, and NR exhibited median total IgE levels (percentage of upper reference value) of 204.0, 65.7, and 16.7, respectively (Table 1). Notably, elevated IgE levels were found in the majority (77.5%) of CR, in 31.8% of PR, and only in 20.0% of NR (chi-squared test, $P < 0.001$) (Figure 1). In contrast, 40.0% of NR showed low normal IgE levels, as compared to 27.3% of the PR and only 2.5% of CR (chi-squared test, $P < 0.005$). The age, gender, or disease duration of patients

with normal and low normal IgE levels did not differ significantly between the three responder groups.

The positive predictive value of elevated total IgE levels, that is, levels higher than the upper reference value, for CR was 75.6%. In addition, the positive predictive value of a total IgE ≤10%, ≤50%, and ≤100% of the upper reference value (normal levels) for non-CR, that is, NR and PR pooled together in one group, was 92.3%, 85.2%, and 75.0%, respectively.

In summary, elevated total IgE levels were common in CR and only rarely detectable in NR to omalizumab. Normal and particularly low normal total IgE levels were prevalent in NR and only rarely detectable in CR. However, normal and low total IgE levels were found in all responder types, and we failed to identify a cutoff for total IgE levels for NR. Accordingly, the total IgE level cannot be used as a stand-alone predictor of response to omalizumab.

Recently, Deza et al⁶ found FcεRI expression levels on basophils before omalizumab treatment to be significantly lower in NR than in responders. They also demonstrated that, after initiation of omalizumab therapy, a significant drop by almost 90% in the basophil FcεRI expression occurred 4 weeks after the first dose with the reduction being lower in NR as compared to responders. In accordance with our work, Deza and coworkers also found that responders present higher total IgE levels at baseline and a positive correlation between IgE levels and basophil FcεRI expression. One possible explanation for these and our findings are that two types of autoimmunity exist in CSU,⁷ that is, type I autoimmunity (driven by IgE autoantibodies against autoantigens)⁸ and type IIb autoimmunity, which is held to be caused by mast cell activating IgG autoantibodies, for example, against the IgE receptor, FcεRI. Indeed, Palacios et al⁹ recently found a link between signs of type IIb autoimmunity and a lower response rate to omalizumab, although their findings were not totally consistent. It may be possible that type IIb autoimmunity and low total IgE levels are linked. Future prospective studies should look at this. Notably, two recently published studies of Ref. 10,11 are also in support of our and the above-mentioned results. Straesser and coworkers reported that patients with low total IgE levels (first quartile) before initiation of omalizumab had a 48% response rate to omalizumab, whereas patients in the second, third and fourth quartile had significantly higher response rates of 86%, 88%, and 94%, respectively.¹⁰ Ertas and coworkers found that nonresponders to omalizumab had significantly lower IgE levels (17.9, 17.0–55.0 IU/mL) than partial responders (82.0, 46.2–126.5 IU/mL) and complete responders (73.7, 19.45–153.8 IU/mL).¹¹

The strength of our study is the multicenter approach and evaluation of patients from all responder groups. The weaknesses are that

TABLE 1 Baseline characteristics

	All patients n = 85	Complete responder (CR) n = 43	Partial responder (PR) n = 23	Nonresponder (NR) n = 19
No. of patients				
Age in years (mean $\pm$ SD, median)	44.3 $\pm$ 15.2, 43	45.6 $\pm$ 15.6, 47	42.7 $\pm$ 14.0, 39	43.3 $\pm$ 16.3, 43 n.s. ^a
Gender (female : male)	67 : 18 (79% : 21%)	35 : 8 (81% : 19%)	17 : 6 (74% : 26%)	15 : 4 (79% : 21%) n.s. ^b
Disease duration in months (median, IQR)	50, 18.0-111.0	53, 24.0-114.0	93, 24.0-147.0	18, 8.0-60.0 P < 0.05 ^c
Total IgE levels in percent of upper reference value (median, IQR)	119.0, 30.1-355.0	204.0, 113.8-437.5	56.7, 9.9-242.0	16.7, 8.4-32.4 P < 0.001 ^c , P < 0.001 ^d , P < 0.05 ^e , P = 0.36 ^f

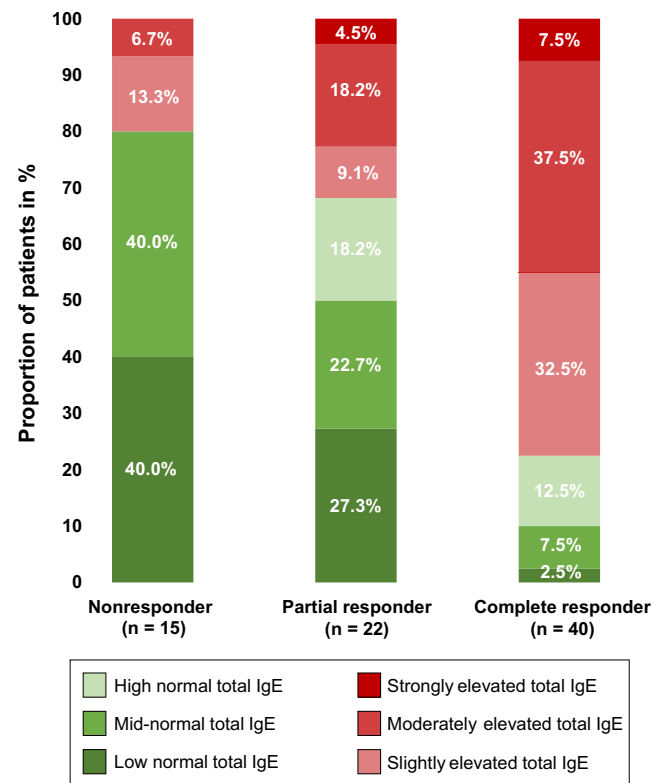
^aComparison of CR, PR, and NR using ANOVA.^bComparison of CR, PR, and NR using chi-squared test.^cComparison of CR, PR, and NR using Kruskal-Wallis test.^dComparison of NR vs CR using Dunn's post hoc test (corrected for multiple comparisons).^eComparison of PR vs CR using Dunn's post hoc test (corrected for multiple comparisons).^fComparison of NR vs PR using Dunn's post hoc test (corrected for multiple comparisons).

FIGURE 1 Response to omalizumab is linked to total IgE levels. Total IgE levels before the initiation of omalizumab were categorized based on their upper reference value into low normal (0%-10%), mid-normal (>10%-50%), high normal (>50%-100%), slightly elevated (>100%-250%), moderately elevated (>250%-1000%), and strongly elevated (>1000%). The proportions of patients with these total IgE level categories are shown for complete responders, partial responders, and nonresponders defined by a reduction in signs and symptoms $\geq 90\%$, $\geq 30\%$ but $< 90\%$, and $< 30\%$ (physicians global assessment), respectively [Colour figure can be viewed at wileyonlinelibrary.com]

the data were analyzed retrospectively, the number of patients included were low, the way of data inclusion carries the risk for a selection bias, the definition of response is based on a physician's global assessment and not backed by urticaria activity score data, and that we could only assess response after 2 injections of omalizumab but not at later time points during treatment.

In conclusion, there is a link between baseline total IgE levels and response to omalizumab treatment in CSU patients, with elevated total IgE levels being frequent in CR but infrequent in NR and normal levels of total IgE being frequent in NR but infrequent in CR.

CONFLICTS OF INTEREST

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Elevated IgE to tissue factor and thyroglobulin are abated by omalizumab in chronic spontaneous urticaria

To the Editor,

Chronic spontaneous urticaria (CSU) is a common condition characterized by episodes of itchy wheals lasting more than 6 weeks.¹ Different biologic systems, that is, autoimmunity, coagulation, and autoallergy, concur to produce CSU symptoms.² The autoimmune mechanism is

based on circulating histamine-releasing IgG autoantibodies to the high-affinity IgE receptor (FcεRI) on both mast cells and basophils or membrane-bound IgE.³ Coagulation cascade is activated in CSU following the hyperexpression of tissue factor (TF) on activated skin eosinophils.^{4,5} The recently identified “autoallergic” mechanism is