Severe CSU with low total IgE levels: is the response to omalizumab always delayed or absent?

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To the Editor

In patients with severe chronic spontaneous urticaria (CSU) Omalizumab represents the treatment of choice if there is no response to H1 antihistamines at higher than licensed dose (1). This anti-IgE mAb is able to induce a rapid drop in UAS7 levels in about 70% of patients and a slower but equally good response over 3-4 months in further 15%. Many studies found a prognostic relationship between baseline total IgE and clinical response to Omalizumab (2-7). The threshold level predicting a non-response or a late response has been detected at < 40 IU/ml in some studies (8) and at 18 IU/ml or less in others (2,3,9). However, based on the clinical response to omalizumab, not all severe CSU patients with low IgE levels seem to have an autoimmune, IgG-mediated (type IIb) disease (10). This retrospective study focused on severe CSU with low total IgE levels and its response to Omalizumab.

Eighty-six consecutive patients (M/F 19/67) with severe CSU (UAS7 > 30) and baseline total IgE levels (measured by commercial ELISA, Thermo Fisher Scientific, Waltham, MA, USA) < 40 IU/ml unresponsive to second generation antihistamines at 3x the licensed dosage and treated with omalizumab 300 mg/month for at least 3 months were studied.

The mean age was 50.5 years (range 7-76), and the disease duration was 41.5 (2-600) months. An UAS7 drop > 50% one month after the first administration were considered as early responders. A drop > 50% from baseline within one month after the 3rd administration was considered as late responders. The absence of any change in UAS7 at month 4 was considered a non-response. The following baseline parameters were assessed: (a) Atopic status (detected by SPT with a large panel of seasonal and perennial airborne allergens [Lofarma, Milano, Italy]; reactivity to at least one allergen was considered a marker of atopy). (b) D-dimer (measured by ELISA [Hyphen BioMed, Neuville sur Oise, France] and considering levels below 500 ng/ml as normal). (c) Thyroid peroxidase (TPO) IgG autoantibodies (measured by ELISA [Thermo Fisher Scientific]; values > 60IU/ml were considered positive. (d) C reactive protein (CRP) (measured by a sandwich immunoassay [Hyphen BioMed]). Proportions were compared by chi-square test with Yates' correction. The internal review board of the Clinic approved this retrospective, observational, anonymous study.

Based on total IgE levels, patients were stratified into 4 subgroups (A, total IgE levels 1-9 IU/ml [n= 28]; B, IgE 10-19 IU/ml [N=24]; C, IgE 20-29 IU/ml [n=22]; and D, IgE 30-39 IU/ml [n=12]). Omalizumab response is shown in table 1 and figure 1. Subgroup A showed the lowest prevalence of early responders (21,4%; $p < 0.005$ vs subgroups B-D) and the highest prevalence of non-responders (64,3%; $p< 0.001$ vs subgroups B-D). Notably, the proportion of unresponsive patients decreased dramatically from subgroup A to D (Figure 1). Prevalence of atopic status, thyroid autoimmunity, positive CRP, and elevated D-dimer are shown in table 1. No statistically significant

difference was found between the 4 subgroups. Since all non-responders were shifted to cyclosporin treatment and responders are still being treated with Omalizumab there were no sufficient data to assess the effect of omalizumab discontinuation and disease relapse.

This study found that many patients with severe CSU and low total IgE levels respond rapidly to Omalizumab. Such proportion exceeded 20% in the subgroup with the lowest IgE levels and ranged between 50% and 68% in the three remaining subgroups. This suggests that also patients with probable type I (autoallergic) CSU may show very low total IgE levels. Mechanisms other than direct IgE binding (including, the down-regulation of IgE receptors on mast cells, and eosinophil apoptosis) may contribute to the efficacy of omalizumab. However, such mechanisms are considered to be associated with a delayed response to omalizumab which was similar in the four subgroups studied here. Although, not surprisingly, the early response rate to omalizumab in these specific patients was lower than that in the general population with CSU, this study suggests that total IgE cannot be considered an absolute predictive marker of response to this drug. In view of its very limited toxicity and reasonable cost, omalizumab should remain stably the third step of CSU management before novel treatments such as Bruton's tyrosine kinase (BTK) inhibitors or anti-Stem cell factor (SCF) mAb that will appear in the next future can be considered.

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Table 1: Clinical response to Omalizumab and clinical and serological variables in patients with severe CSU stratified by total IgE levels

Subgroup	Early response	Late response	Non-response	Atopic status	Elevated CRP	Thyroid autoimmunity	Elevated D-dimer
A (n=28)	6 (21.4%)*	4 (14.3%)	18 (64.3%)**	2 (7.1%)	9 (32%)	10/26 (38.5%)	13/24 (54.1%)
B (n=24)	14 (58.3%)	5 (20.8%)	5 (20.8%)	5 (20.8%)	5 (20.8%)	3/23 (13%)	8/17 (47.1%)
C (n=22)	11 (50%)	6 (27.2%)	5 (22.7%)	3 (13.6%)	4 (18.2%)	10/22 (45.4%)	7/20 (35%)
D (n=12)	8 (66.6%)	3 (25%)	1 (8.3%)	3 (25%)	1 (8.3%)	1/11 (9.1%)	4/11 (36%)

*p< 0.005 for subgroup A vs B+C+D; **p< 0.001 for subgroup A vs B+C+D

Figure 1: Omalizumab response in the 4 subgroups of patients with severe CSU