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Clinical variables of severe chronic spontaneous urticaria from total IgE standpoint: a retrospective study

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KEY WORDS

Urticaria; IgE; omalizumab; thyroid autoimmunity; D-dimer; atopy.

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IMPACT STATEMENT

CSU patients showing total IgE levels of 18 IU/ml or less are unlikely to respond to omalizumab. Most CSU patients show a mixed picture of atopic status and signs of autoimmune disease.

Summary

Background. Baseline total IgE levels have recently emerged as a prognostic factor for the clinical response to omalizumab in patients with severe chronic spontaneous urticaria (CSU). **Objective.** To investigate the main clinical features of patients with severe CSU from the standpoint of baseline total IgE. **Methods.** 153 patients (M/F 52/101; mean age 49.7 years) with severe CSU were studied. Based on IgE levels patients were divided into 5 subgroups and a ROC curve was built to define a threshold level for omalizumab response. Atopic status, thyroid autoimmunity, activation of the coagulation cascade, and response to omalizumab were studied as well. **Results.** The subgroups did not differ in terms of age and gender. Atopy prevailed in the subgroup showing elevated IgE. Thyroid autoimmunity and elevated D-dimer levels were similarly distributed in the five subgroups. 94 patients showed a prompt response to omalizumab. The likelihood of a prompt response was higher in males ($p < 0.01$). In the subgroup showing the lowest IgE levels only 10% responded promptly to the drug; these proportions were 60%, 65%, 81% and 83% in the remaining groups. 66% of those in group A did not respond at all to omalizumab. A threshold IgE level of 18 IU/ml was detected for omalizumab response. **Conclusions.** Baseline total IgE show a high prognostic value for omalizumab response with a threshold level of 18 IU/ml. Males seem more responsive to omalizumab. Most patients show a mixed clinical picture where signs of atopic status co-exist with signs of an autoimmune disease.

Introduction

Chronic spontaneous urticaria (CSU) affects about 1% of the general population and its severity shows much variability. In severe cases, second-generation antihistamines are unable to control the disease and omalizumab or cyclosporine are needed as add-on therapy (1). Recently, the relevance of elevated baseline total IgE levels as a prognostic factor for the clinical response to omalizumab emerged (2) supporting a possible IgE-mediated autoimmune pathogenesis (3). On the other hand, patients showing an IgG-mediated autoimmune disease show low IgE and elevated thyroid autoantibodies (4). The present study investigated the main clinical features of patients with severe CSU from the standpoint of baseline total IgE.

Methods

153 consecutive patients (M/F 52/101; mean age 49.7 years; range 12-89 years) with severe CSU unresponsive to antihistamines were included. The mean disease duration was 51.7

months (range 2-720 months), and baseline UAS-7 level was > 28 in all cases. Baseline IgE were measured (normal if < 100 IU/ml). In the attempt to detect an IgE cutoff level able to predict the lack of response to omalizumab, differently from Straesser *et al.* (2) who performed a quartile analysis, patients were arbitrarily divided into 5 subgroups of comparable size 3 of whom showed normal IgE levels: A) 0-20 UI/ml ($n = 29$); B) 21-50 UI/ml ($n = 30$); C) 51-100 UI/ml ($n = 20$); D) 101-200 UI/ml ($n = 26$); and E) > 200 IU/ml ($n = 48$). Further, a ROC curve was built in order to add more information on the predictive value of IgE and to define a threshold predicting the response to the treatment.

Other variables investigated at baseline included:

1. atopic status, detected by positive skin prick tests (SPT) with commercial airborne and/or food allergens (Lofarma, Milan);
2. thyroid autoimmunity;
3. activation of the coagulation cascade (D-dimer plasma levels positive if > 500 ng/ml).

Responses to omalizumab 300 mg/month were classified as:

- early/complete (UAS-7 level 0-7 < 1 month after the first administration);
- late/complete (UAS-7 level of 0-7 < 3 months after the first administration);
- partial (UAS-7 reduced by > 50% but still > 7 at month 3);
- absent (UAS-7 unchanged at month 3).

Following the current Italian legislation, patients unresponsive after 3 months had to stop the treatment, and were offered cyclosporine treatment. The internal review board of the clinic approved this retrospective study.

Results

The clinical features of the five subgroups of patients are summarized in **table I**. The five subgroups did not show significant differences in age and gender distribution. Atopy ranged between 17% and 27% in subgroups A-D and peaked to > 50% in subgroup E. Thyroid autoimmunity was found in 14%-37% of the subgroups and did not show any significant association with total IgE levels. D-dimer plasma levels were elevated in > 36% of patients in all subgroups and were not associated with any specific subset.

Omalizumab response is summarized in **figure 1**. A total of 94 patients showed an early/complete response to the drug whereas the remaining 59 showed a slow response or did not respond at all. The proportion of early complete responders was significantly higher among male patients than among female patients (40/52 (77%) vs 54/101 (53%); $p < 0.01$ chi square test with Yates' correction). The response to the drug was early/complete in 10% in subgroup A patients, and increased to 60%, 65%, 81% and 83% in groups B-E, respectively, whereas the treatment failed in 66% of subgroup A, but only in 13%, 10%, 4%, and 2% in subgroups B-E, respectively. Few patients in all subgroups showed a delayed or partial response to omalizumab (data not shown). Group A Patients showing an early/complete response to omalizumab showed an IgE level of 16, 16 and 18 UI/ml, respectively. Among patients with elevated IgE levels

(groups D and E) non-responders to omalizumab did not show any remarkable difference from responders in terms of age, sex, atopy, or thyroid disease.

The ROC curve is shown in **figure 2**. An AUC of 0.84 was detected showing a significance level < 0,0001. A threshold IgE level of 18 was found for omalizumab response (95% IC 9-67). Cyclosporin treatment was eventually started 16/30 (53%) non-responders to omalizumab. The relative proportions in subgroups A-E were 65% (11/17), 40% (2/5), 50% (2/4), 100% (1/1), 0% (0/2), respectively.

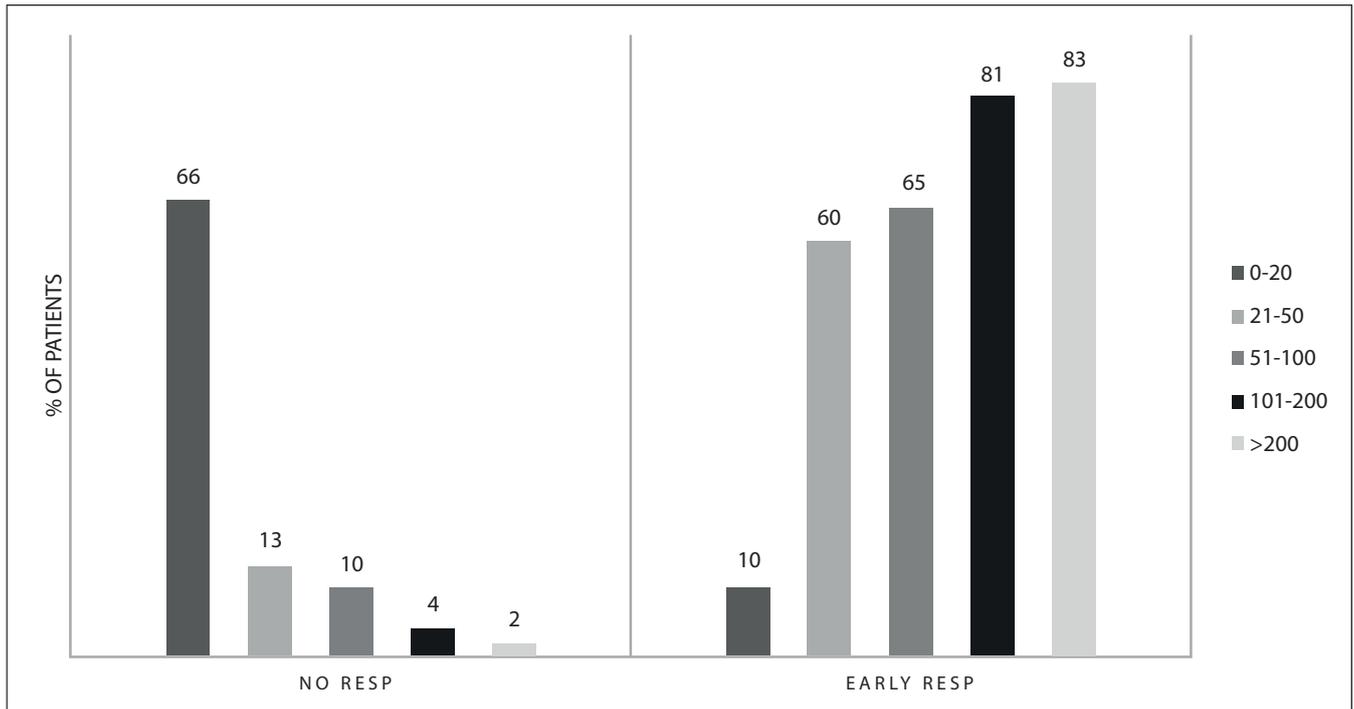
Discussion

This study shows once more the high prognostic value of baseline total IgE levels for omalizumab response although some patients with elevated total IgE (*i.e.*, > 100 IU/ml) did not respond and about 10% of those with total IgE < 20 IU/ml did. Partial and late responders were few and uniformly distributed through the subgroups. Some patients classified as non-responders might have been late responders but in Italy it is not allowed pursuing omalizumab treatment beyond three months in the absence of a significant clinical response. In this study population the large majority of non-responders was found in subgroup showing IgE levels lower than 20 UI/ml; in fact, those included in this subgroup showed a 66% probability to not respond to omalizumab treatment. In the immediately subsequent subgroup (that of patients showing total IgE levels ranging between 21 and 50 IU/ml) things were completely different and the percentage of a prompt response to omalizumab rose dramatically to 60%, increasing further in the following subgroups. The ROC curve identified an IgE threshold of 18 IU/ml. These observations fully confirm those by Straesser and coworkers (2) who, dividing patients into quartiles based on IgE levels, detected the (very similar) threshold of 15.2 IU/ml, and also those by Weller *et al.* (9) who approached the problem of total IgE levels (detected by different methods in a multicenter study) as percentages of the upper reference value, finding that most non-responders showed "low normal" IgE (*i.e.*, 0%-10% of the normal range).

Table I - Clinical features of CSU patients in the five subgroups based on total IgE levels.

Groups	A	B	C	D	E
No.	29	30	20	26	48
M/F	6/23	7/23	5/15	13/13	21/27
Mean Age (range)	48.9 (12-77)	48.7 (19-72)	51.6 (25-70)	52.4 (16-76)	48.7 (14-89)
Atopy	5 (17%)	4 (13%)	4 (20%)	7 (27%)	25 (52%)
Thyroid disease	5/27 (19%)	10/28 (36%)	7/19 (37%)	5/24 (21%)	6/44 (14%)
Elevated D-dimer	14/27 (52%)	10/28 (36%)	6/16 (38%)	10/24 (42%)	20/39 (51%)

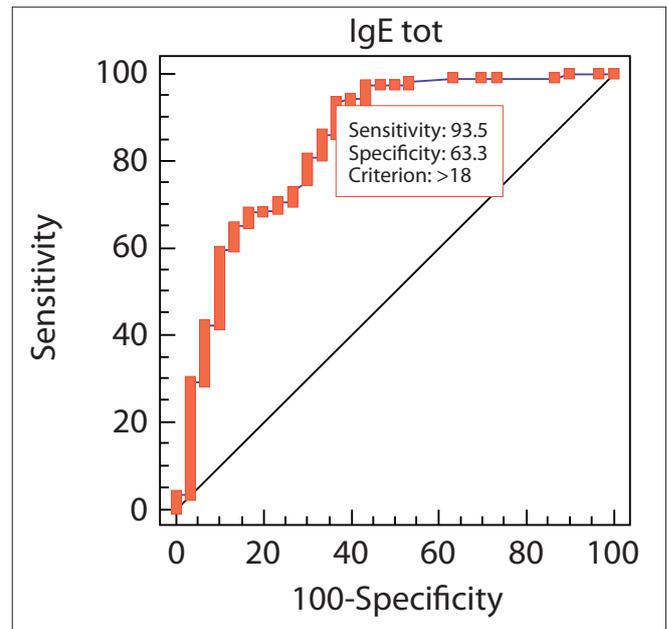
Figure 1 - Response to omalizumab in patients divided based on total IgE levels.



No resp: no response to omalizumab after 3 months of treatment. Early resp: full response to omalizumab after as early as 1 month after the first administration.

Finally, Ertas *et al.* (10) also found that non-responders to omalizumab showed a mean baseline IgE level of about 18 IU/ml. Another interesting point that confirms an observation by Straesser *et al.* is that male patients seem to show a greater likelihood to respond to omalizumab treatment (2). The reason for this is unclear, although one could speculate that in general most IgG-mediated autoimmune disorders show a higher prevalence of female patients. Not surprisingly, atopy paralleled total IgE levels although more than 10% of patients showing normal IgE levels were atopic. The well-known association between CSU and thyroid autoimmunity (5) was fully confirmed here. However, the similar prevalence of patients showing thyroid autoimmunity in the five subgroups suggests that in this population, as a difference from the study by Schoepke *et al.* (4), such phenomenon appears to be independent on a specific underlying pathogenic mechanism. Elevated D-dimer plasma levels were frequently found and equally distributed in the 5 subgroups which is not surprising as the whole study group was made up of patients with severe CSU (6), but this also suggests that the activation of the coagulation cascade may occur irrespective of the pathogenic mechanism (7). Altogether, importantly, this study shows that CSU patients show in most cases a mixed clinical picture where signs of atopic

Figure 2 - ROC curve showing the predictive role of IgE and the threshold level for omalizumab response.



status co-exist with signs of an autoimmune disease. In effect, in previous studies (4) only a small minority of CSU patients showed a clear-cut IgG-mediated autoimmune picture based on three distinct parameters suggesting that in most cases the pathogenesis probably is a mixed one (8).

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Conflict of interests

The author declares that he has no conflict of interests.

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