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The autologous serum skin test predicts the response to anti-IgE treatment in chronic spontaneous urticaria patients: a prospective study

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KEY WORDS

Chronic spontaneous urticaria; autologous serum skin test; omalizumab; IgE; endotype.

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IMPACT STATEMENT

In patients with chronic spontaneous urticaria a positive autologous serum skin test is strongly associated with a good but delayed response to omalizumab.

Summary

Background. Chronic spontaneous urticaria (CSU), characterized by recurrent itchy wheals and angioedema for > 6 weeks, is a quite common disease that may heavily impair the quality of life. Omalizumab, an anti-IgE mAb, has much improved the management of CSU but patients' response to the drug may vary and predictive markers are still largely missing. We investigated the predictive value of the autologous serum skin test (ASST) on omalizumab response. **Methods.** 15 patients with severe CSU eligible for omalizumab treatment were prospectively studied submitting them to ASST and to complete blood count, D-dimer, anti-thyroid peroxidase antibodies, and total IgE measurement before the start of the treatment. **Results.** 14/15 (93%) responded brilliantly to omalizumab at 3 months assessment. 7 responded in less than 1 month ("early responders") and 7 only after multiple administrations ("late responders"). Of 9 patients scoring positive on ASST, 7 (78%) were late, and 2 (22%) early responders to omalizumab ($p = 0.021$). Of 6 patients scoring negative on ASST, 5 were early omalizumab responders and 1 did not respond. The PPV and NPV of the ASST for a "late" response to omalizumab were 78% and 100%, respectively. Total IgE were significantly higher in early responders. **Conclusions.** Although larger prospective studies are needed to confirm these results, this study confirms previous retrospective investigations that the positive ASST appears to predict a slow response to omalizumab in CSU patients.

Introduction

Chronic spontaneous urticaria (CSU), defined as the recurrent occurrence of itchy wheals often with angioedema for more than six weeks, is a common disease that may heavily impair the quality of life. More than 30 years ago, Grattan and co-workers (1) found that a significant proportion of CSU patients respond with a wheal-and-flare reaction at the site of the intradermal injection

of a small amount of autologous serum (autologous serum skin test, ASST). This observation represented the first step towards a better understanding of the pathogenesis of chronic spontaneous urticaria (CSU) as an autoimmune disease. The clinical significance of ASST as well as its methodology and interpretation were reviewed and defined by task forces of the European Academy of Allergy and Clinical Immunology (EAACI) about 15 years ago (2, 3). The task forces stated that, although its neg-

ative predictive value is high, the ASST should be regarded as a test for autoreactivity rather than a specific test for autoimmune urticaria, as it shows only moderate specificity as a marker for functional autoantibodies against IgE or the high-affinity IgE receptor (FcεRI) (2).

Omalizumab, an anti-IgE mAb, has been the second-line therapy for antihistamine-refractory CSU since 2014 (4). Despite its generally high efficacy, variability in patient response to this biological therapy has been evident since the start of its use, with most patients experiencing symptom control, either promptly or after several months of treatment, and a small subset showing only partial response or no response at all.

Although the ASST has been considered a possible marker of IgG-mediated (type IIb) autoimmune CSU along with the direct detection of IgE and FcεRI autoantibodies (5), no study so far investigated prospectively its possible predictive value in the light of omalizumab response. In the present study, we addressed the predictive significance of ASST for omalizumab response in patients with severe CSU.

Materials and methods

We performed a prospective study aiming to assess the predictive value of the ASST on the clinical response to omalizumab in patients with severe urticaria. To this end, 15 adult patients (aged between 18 and 75 years and with a disease duration ranging from 6 weeks to > 10 years) with severe CSU eligible for omalizumab therapy were recruited from the allergology outpatient clinics of the Department of Internal Medicine and Clinical Immunology and the Dermatology Department of Policlinico Umberto I in Rome between October 2022 and August 2023. The study participants, all refractory to second-generation antihistamines at higher than licensed dosage (4), signed an informed written consent to undergo the ASST before starting the biological treatment. The autologous serum skin test was performed and read following the current recommendations, and was classified as positive or negative (2, 3). UAS7 was assessed at baseline when it exceeded a value of 30 in all cases, and then monthly after the

start of omalizumab treatment. Upon enrollment, patients underwent also complete blood count, as well as D-dimer, anti-thyroid peroxidase antibodies, and total IgE measurements.

Omalizumab was administered at a monthly fixed dose of 300 mg and had to be stopped in case of no response after 3 months of treatment, as per the current Italian legislation. Patients were classified as “early responders” if they showed a drop of UAS7 to < 16 one month after the start of the treatment, “late responders” if such drop of UAS7 was detected within 3 months of treatment, or non-responders if no significant change in UAS7 was detected after 3 administrations of omalizumab.

Results were analyzed SPSS version 27.0 and JASP version 0.18.1.0. A confidence interval of 95% was set, and correlations were considered significant at a P-value below 0.05. Specific tests such as Fisher's exact test, Student's t-test, PPV, NPV, and logistic regression models were employed as appropriate.

The study was approved by the Ethical Committee of the Policlinico Umberto I in Rome (ID 7097 prot. 0366/2023).

Results

Results are summarized in **table I**. Of the 15 patients studied, 14 (93%) exhibited a clear clinical benefit 3 months after the start of omalizumab treatment while 1 patient (7%) was classified as “non-responder”. Of the 14 omalizumab responders 7 (46.5%) responded already after the first administration (“early responders”), and 7 (46.5%) responded only after multiple administrations, (“late responders”).

Nine patients (60%) scored positive on the ASST, while 6 (40%) scored negative. Grouping patients based on omalizumab response, 5/6 ASST-negative individuals responded promptly to the drug, and 1/6 did not show any response, whereas 7/9 (77%) ASST-positive patients were “late responders” and 2/9 (22%) exhibited an “early” response ($p = 0.021$). The PPV and NPV of the ASST for a “late” response to omalizumab were 78% and 100%, respectively. The “early response” group showed a mean total IgE value of 601 kU/L (IQR 458-813), while in the “late” response group mean total IgE was 50 kU/L (IQR 14.5-180) ($p = 0.029$). This result

Table I - Summary table of the differences between the means of the two groups of patients divided according to the response to therapy.

	t	df	p	Mean difference	SE difference	95%CI for mean difference	
						Lower	Upper
D-dimer (ng/ml)	1.366	12	0.197	658.571	482.291	392.251	1.709.393
Total serum IgE (kU/l)	2.348	12	0.037	415.171	176.815	29.924	800.419
Eosinophils (cells/μl)	0.322	12	0.753	31.429	97.485	180.974	243.831
Anti-TPO IgG (UI/ml)	-1.629	12	0.129	-33.286	20.438	-77.817	11.245

Student's t-test.

was confirmed also by Student's t-test ($p = 0.037$) (**table I**). The other continuous variables investigated did not differ significantly between the two groups (**figure 1**).

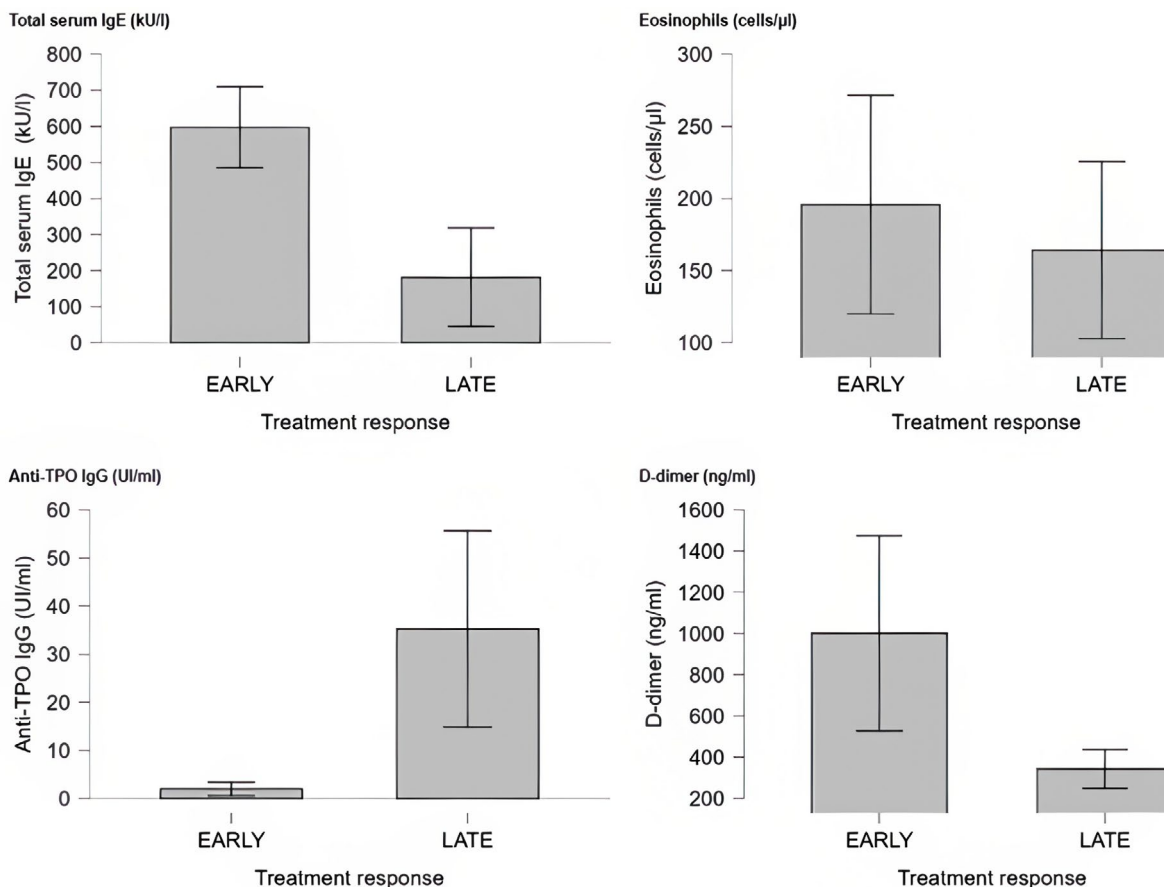
The only patient who did not show any response to omalizumab scored negative on ASST, and showed a low total IgE level (31.6 UI/ml), as well as negative D-dimer, TPO IgG, and a normal Eosinophil count.

Discussion and conclusions

The present prospective study confirmed the efficacy of Omalizumab in the treatment of CSU (6, 7), and the association between elevated total IgE and a faster response to the therapy (8). In a recent review article, Fok and coworkers (9) remarked that the data of the link between ASST and omalizumab response are still inconsistent, and that prospective studies are needed to confirm it. We observed that most of our patients showing a wheal-and-

flare skin response upon the injection of autologous serum were eventually classified as "late responders" to omalizumab, thus fully confirming in a prospective fashion previous observations by Gericke *et al.* (10) who found that ASST-positive CSU patients were 5.5 times more likely to show a slow response to omalizumab than ASST-negative patients, and by Nettis *et al.* (11), whose patients with a positive autologous serum skin test (ASST) were significantly more likely to be "slow responders" to omalizumab treatment. Similar results were also obtained by Chinese researchers in their population (12). Interestingly, only a minority of our "early" omalizumab responders scored positive on ASST. Since an early response to anti-IgE therapy has been associated with type I ("autoallergic") CSU, which is most likely characterized by the presence of IgE specific for several potential auto-allergens, our findings seem to suggest that the ASST does not score positive in the presence of circulating, autoreactive IgE. In contrast, a positive ASST seems to identify patients with IgG-me-

Figure 1 - Graph of the different means with confidence interval of the continuous variables examined in this study in the two groups divided by treatment response.



diated autoimmune (type IIb) CSU, characterized by IgG specific for IgE or for high-affinity IgE receptor, in whom the late response to omalizumab is possibly based on a slow downregulation of the IgE-receptor expression on mast cell surfaces (13). The observation of a positive ASST in some early responders might be due to the co-occurrence of auto-reactive IgG and IgE (14). Another interesting point is that the only patient refractory to omalizumab treatment scored negative on the ASST and showed low total IgE, thus showing a discrepancy between the predictive value of these two biomarkers.

The prevalence of positive ASST has been extremely variable throughout the various studies of CSU (15) possibly due to differences in populations studied, and positive ASST results have been frequently recorded also in patients with conditions other than CSU (16). Nonetheless, one point that has been always clear is that the ASST scores positive only in a proportion of CSU patients and that it only partially overlaps with the direct measurement of IgG autoantibodies to the high affinity IgE receptor or IgE (5) or with the basophil histamine release assay (17). Now, in the light of the recent findings about the different endotypes of CSU, these older “strange” observations appear much clearer. Altogether, our findings suggest that the ASST maintains its clinical validity both in detecting patients with a probable IgG-mediated autoimmune pathogenesis and in predicting a late response to omalizumab.

The main limitation of this study is certainly its reduced sample size. Nonetheless, all the main data, including the significantly higher total IgE levels in early responders, the proportion of patients scoring positive on ASST, and the proportion of positive omalizumab responses observed were perfectly in line with those found in most previous studies, thus substantiating our conclusions. Further, although larger prospective studies will undoubtedly be necessary to confirm our observations, the results of this study confirmed those of other observational retrospective ones (10-12) and were so clear-cut to demonstrate statistically significant differences even in the presence of a population as small as 15 individuals.

Fundings

None.

Contributions

AP, FV, EP, MV: data curation, formal analysis, investigation, writing - review & editing. RA: conceptualization, methodology, project administration, writing - original draft, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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