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Omalizumab in severe chronic urticaria: are slow and non-responders different?

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KEY WORDS

Chronic Urticaria; omalizumab; biomarkers; IgE; thyroid autoimmunity.

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Doi

10.23822/EurAnnACI.1764-1489.167

Summary

Background. The response to omalizumab by patients with severe chronic spontaneous urticaria (CSU), may be rapid, slow, or absent. An early response has been associated with an IgE-mediated auto-allergic pathogenic mechanism, whereas little is known about slow and non-responders. **Objective.** To compare CSU patients responding slowly or non-responding to omalizumab. **Methods.** Forty-six patients showing a slow ($n = 23$) or absent ($n = 23$) response to omalizumab out of a cohort of 170 patients with severe CSU (UAS-7 > 30) were studied. Several baseline clinical and serological parameters were compared in the two groups. **Results.** Apart from a lower prevalence of atopic diseases ($p < 0.05$) and a slightly higher prevalence of thyroid autoimmunity in non-responders, the two groups were similar in terms of clinical and serological features. The majority of patients in both groups showed low baseline total IgE levels. **Conclusions.** Patients with severe CSU showing a slow response or not responding at all to omalizumab show impressive similarities. It is currently not possible to predict whether patients with severe CSU and low IgE levels will show a slow response or will not respond to anti-IgE treatment.

IMPACT STATEMENT

CSU patients responding slowly or not responding to omalizumab are very similar, the latter showing only a lower prevalence of atopic diseases and a slightly higher prevalence of thyroid autoimmunity. At baseline it is currently impossible to predict their response to omalizumab.

Introduction

Omalizumab has become an essential treatment for patients with chronic spontaneous urticaria (CSU) unresponsive to antihistamines even at higher than licensed doses (1). Anti-IgE is able to induce a rapid drop in UAS7 levels in about 70% of cases (the so-called early or fast responders) and a slower but equally good response over 3-4 months in further 15% of patients (the so-called late or slow responders; the remaining 15% seem refractory to the treatment (2). Recently, several studies showed a relationship between baseline total IgE levels and the clinical response to the drug (3, 4). With the possible confounding factor of atopic status (5), average baseline total IgE levels are

significantly lower in patients unresponsive to omalizumab than in those partially or totally responsive to the drug. The detection of an IgE-mediated, "auto-allergic" pathogenic mechanism in a large proportion of CSU patients represents a reasonable explanation for a rapid response to omalizumab by severely affected patients (6). In contrast, much less clear are the events occurring slow- and non-responders. A recent international, multicenter study (7) was able to identify a specific subset of patients showing several signs of IgG-mediated autoimmunity, including IgG specific for the high affinity IgE receptor (FcεRI) or for IgE, which were characterized by low total IgE levels. Nonetheless,

also these subjects might show a good, albeit frequently slow, response to omalizumab in view of the multiple effects of this drug which include among the others a down regulation of high affinity IgE receptor on mast cells and basophils (reviewed in ref. #8). To the best of our knowledge, CSU patients showing a slow response to omalizumab or not responding at all to the drug have not been analyzed vis-a-vis so far. The present study analyzed and compared a series of clinical and serological features in these two subsets of patients with CSU.

Methods

The starting general population was represented by a group of 170 patients with severe CSU (UAS-7 > 30) unresponsive to second generation antihistamines at higher than licensed doses submitted to omalizumab 300 mg/month for at least 3 months. One-hundred-twenty-four patients showed a prompt response to the drug (*i.e.*, a drop of UAS-7 > 50% one month after the first administration) and were excluded from the study. Sixty-three randomly selected subjects from this group were used as control group. The remaining 46 patients (M/F 13/33) who did not show any response 1 month after the first administration were studied. Based on their subsequent response to omalizumab, which was assessed one month after the third administration, patients were classified as late responders (showing a drop > 50% of baseline UAS-7 levels; n = 23) or unresponsive (no change in urticaria activity; n = 23). The need to evaluate patients after 3 administrations comes from the current Italian legislation that forbids to continue omalizumab administration beyond 3 months in the absence of any response. The two subgroups were compared for age, sex, disease duration, and for a series of baseline laboratory parameters including ESR, CRP, thyroid auto-

immunity, total IgE, D-dimer, and atopic status. Atopic status was detected by SPT with a large panel of commercial extracts of both seasonal and perennial respiratory allergens (Allergopharma, Reinbeck, Germany) that were carried out and read following established methods (9). The chi-square test with Yates' correction, the two-tailed Student's t-test, or the Mann-Whitney non-parametric test were employed to compare the two study groups where appropriate. Probability values < 5% were considered statistically significant. The study was approved by the internal review board, and all the patients signed an informed consent to use their clinical data in an anonymous form.

Results

Table I summarizes the findings in the two study groups and in the control group. The two subsets did not differ in gender, age, disease duration, prevalence of elevated CRP, ESR, D-dimer, thyroid autoimmunity, and total IgE levels. Further, no patient in the two groups showed sign of co-existing inducible urticaria. Patients unresponsive to omalizumab showed a 3 times higher prevalence of thyroid autoimmunity than late responders (9/21 [42%] *vs* 3/22 [14%]; NS). In contrast, atopic status was more frequent among late responders (9/23 [39%] *vs* 2/23 [9%]; p < 0.05). Notably, the control group (*i.e.*, the early omalizumab responders) showed a prevalence of atopic status and of thyroid autoimmunity that was more similar to late responders than to non-responders. Total IgE levels were well below the normal range (*i.e.*, < 50 UI/ml; normal cut-off level 100 UI/ml) in the large majority of patients (23/34 [68%]) with an equal distribution between non-responders (14/18 [77%]) and slow responders (9/16 [56%]). Median total IgE levels were 42 UI/ml (5 – 1000) and 9 UI/ml (1-264) in late responders and non-responders, respec-

Table I - Comparison between the baseline clinical and serological characteristics of the study populations.

	Late responders (n = 23)	Non responders (n = 23)	p	Controls (Early responders) (n = 63)
Age (median and range)	53 (12-78)	54 (16-77)	NS	52 (13-89)
Sex (M/F)	9/14	4/19	NS	31/32
Median Disease Duration (mo)	10 (2-300)	9 (2-500)	NS	9 (2-600)
Positive CRP	4 (20%)	7 (30%)	NS	10 (16%)
Positive ESR	3 (19%)	6 (27%)	NS	2 (3%)
Atopic status (%)	9 (41%)	2 (9%)	< 0.05	21 (33%)
Median total IgE (UI/ml)	42 (5 – 1000)	9 (1-264)	NS	184 (16-1139)
Elevated D-dimer	11/22 (50%)	12/21 (57%)	NS	22/51 (43%)
Median D-dimer (ng/ml)	493 (159-2455)	658 (190-2500)	NS	487 (160-3700)
Thyroid autoimmunity	3/22 (14%)	9/21 (42%)	NS	12/57 (21%)

tively. The difference, albeit clear, did not reach the statistical significance. In contrast, the control group showed a much higher level of baseline total IgE than both study groups. In total, 7 patients showed total IgE levels exceeding 100 UI/ml; of these, 5 were atopic: 2/2 in the non-responders group and 3/5 in the slow responders group. After the exclusion of atopic patients, the maximum value of total IgE recorded among non-responders was 67 UI/ml, whereas among late responders values ranged between 5 IU/ml and 442 IU/ml.

Discussion

This is the first study comparing two minority subgroups of patients with severe CSU identified by their response to anti-IgE therapy, namely those unresponsive and those showing a slow response to omalizumab 300 mg/month for 3 months. Taken together, these two subgroups represent about 30% of patients with severe CSU undergoing anti-IgE treatment. It must be admitted that the present study might show a partial classification bias. In fact, in some cases the response to omalizumab may become clinically apparent after more than 3 months of treatment; unfortunately, the current Italian legislation does not allow pursuing the treatment beyond 3 months in the absence of any appreciable clinical benefit. Therefore, it is possible that some patients that were eventually included among non-responders were in effect very slow omalizumab responders. Another possible bias is that some patients might have responded to higher doses of omalizumab (10). However, again the current Italian rules do not allow increasing the dosage of omalizumab in the absence of a clinical response at 300 mg/month. Also in this case it is possible that some omalizumab responders were mistakenly classified as non-responders. However, in previous studies up dosing of omalizumab was mostly successful in subjects showing a partial response at 300 mg/month, which was not the case in the patients studied here.

The most interesting finding of this study is the similarity between these two subgroups of urticaria patients in terms of both clinical and serological features. Non-responders showed a higher prevalence of thyroid autoimmunity, although this was statistically non-significant). Interestingly, there was a higher prevalence of atopic patients among late omalizumab responders, which is a novel finding. This might partially explain the different outcome, since omalizumab in atopic subjects might have enough IgEs to bind to produce a non-specific downstream effect in FcεRI-bearing cells to which urticaria patients could partially benefit from. In effect late responder patients were quite similar to the control group (*i.e.*, early omalizumab responders) in terms of both atopic status and thyroid autoimmunity. With the exception of atopic subjects, most patients in the two groups showed very low total IgE levels, which is in keeping with the observed association between elevated IgE levels and a rapid response to anti-IgE treatment in CSU (3, 4, 11). In effect, in

a recent study comparing CSU patients showing a rapid or a low response to omalizumab the former showed a much higher prevalence of elevated total IgE (12). Both groups studied here resembled those CSU patients with several signs of IgG-mediated autoimmunity investigated in the PURIST study, who also showed low total IgE levels and a high prevalence of thyroid autoimmunity (7). Of course, possible differences between the two groups in parameters that were not considered here cannot be ruled out. For instance, it would have been interesting to perform a basophil activation test or the measurement of FcεRI, but these methods were not routinely available.

A rapid response to omalizumab occurs in the majority of patients with severe CSU, possibly as the result of the blockade of autoreactive IgE (both circulating and bound to the high affinity IgE receptor on effector cells) by IgG-anti-IgE antibodies (6, 8). The events leading to a slow response or to the non-response to the drug are less clear. In patients showing low total IgE levels and an IgG-mediated autoimmune process able to activate mast cells and basophils via the high affinity IgE receptor, either directly (by IgG-anti-FcεRI) or indirectly (by IgG directed against receptor-bound IgE) (13, 14), the effect of omalizumab might rely on the down-regulation of IgE receptors, a process that would take some months of treatment to occur (8). Of course, other mechanisms might also play a role in these subjects, including a reduction in mast cell releasability, an improvement of basophil IgE receptor function, or a reduction of the activity of intrinsically 'abnormal' IgE (8). In non-atopic patients showing elevated IgE, a slow response to the drug might be due to the contemporary presence of IgE and IgG-mediated autoimmunity (15). In contrast, the complete absence of response to omalizumab might suggest a pathogenesis that does not involve at all (*i.e.*, bypasses) the high affinity IgE receptor. In effect, some studies demonstrated the presence of circulating, low molecular weight histamine releasing factors able to induce the degranulation of a human mast cell line missing the FcεRI receptor in the sera of CSU patients (16, 17). Further, Ertas and co-workers, following-up their CSU patients treated with omalizumab found that in non-responders the drug administration did not cause any increase in total IgE levels (4), which is a common finding in patients treated with this drug.

Conclusions

In conclusion, slow and non-responders to omalizumab 300 mg/month show impressive clinical and serological similarities, including low total IgE levels. Therefore, it is currently not possible to predict whether patients with severe CSU and low IgE levels will show a slow response or will not respond to anti-IgE treatment.

Conflict of interests

The author declares that he has no conflict of interests.

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