

The percentage of patients achieving complete remission of urticaria increases with repeated courses of treatment

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Clinical Implications

- Omalizumab displays high clinical efficacy in patients with urticaria. The demonstration that the percentage of patients achieving complete remission of urticaria increases with repeated courses of treatment suggests that omalizumab therapy should be extended over a long period of time.

TO THE EDITOR:

Omalizumab, a humanized monoclonal IgG antibody targeting free IgE, is effective in patients with chronic spontaneous urticaria (CSU).¹

After receiving informed consent, 30 patients suffering from CSU not responding to H₁-antihistamines were treated with omalizumab (300 mg/4-week intervals for 6 administrations). Fourteen patients (46.7%) displayed urticaria despite oral steroid treatment (mean dose 5.4 ± 0.5 mg/day). Angioedema was present in 56.7% (17 of 30) of the patients. Patients were classified as responders when, during the treatment, the urticaria activity score (UAS) was <2 and UAS7 <7; nonresponders when the UAS and UAS7 did not change significantly; and partial responders when the UAS was reduced, but UAS was ≥2 and UAS7 ≥7. After the end of treatment, patients were monitored every 2 months and those who relapsed were retreated with the same protocol; in case of a second relapse, a third additional treatment was performed.

All patients were submitted to intradermal autologous serum skin testing (ASST); antinuclear antibody (ANA) detection; and total and specific IgE levels for a panel of aeroallergens and foods. Antiomalizumab antibodies were measured by a homemade double bridging ELISA assay. Statistical analysis was performed using Student's *t* test and Fisher's exact test. Table I summarizes patients' clinical characteristics.

We observed a significant reduction of both UAS (4.4 ± 0.2 vs 0.4 ± 0.2, *P* < .0001) and UAS7 (26.9 ± 1.2 vs 3.6 ± 1, *P* < .0001), evaluated after 6 months of therapy. In particular, 25 of 30 patients (83.4%) were responders, 4 (13.3%) were partial responders, and 1 (3.3%) did not respond. Among 29 patients, 2 (6.9%) were able to interrupt and 16 (55.1%) to reduce H₁-antihistamine treatment. Among patients receiving steroid therapy, 9 of 14 (64.2%) stopped the treatment; 3 (21.4%) reduced the daily dose. Mean time to achieve a partial or complete response was approximately 5.8 ± 1 weeks. Of note, in 8 of 29 patients (27.5%), a very early onset of response

TABLE I. Patients' characteristics at baseline

Characteristic	n = 30
Gender (F/M)	22/8
Age (x-y, y)	20-70; 47 ± 2.6
Disease duration (y)	6 ± 1
Urticaria	13 (43.4%)
Urticaria + angioedema	17 (56.7%)
Total IgE (kU/L)	227 ± 42.8
Atopic status*	7 (23.3%)
Positive ASST	9 (30%)
ANA positivity	7 (23.3%)
Medication use	
H ₁ -antihistamine	30 (100%)
Corticosteroid	14 (46.6%)

ANA, Antinuclear antibodies; ASST, autologous serum skin test.

*Sensitization to inhalant and/or food allergens.

(UAS < 2) occurred, a few days after the first administration. Ten patients (34.5%) showed an early response within the first 2 to 4 weeks. A late response (≥12 weeks) was observed in 6 patients (20.7%). In agreement with others, we observed no difference in terms of rapidity or degree of response in ASST, correlating with ANAs or atopic status.²

Of 29 patients (11 complete remission; 14 responders without remission; 4 partial responders), 24 were monitored for length of response after omalizumab interruption. In 5 patients (17.2%), this monitoring was not possible and they were excluded from the analysis. The majority of patients (19 of 24; 79.1%) displayed a relapse of urticaria (mean time 12.5 ± 4.0 weeks). Symptom severity was similar to that displayed before the treatment (UAS [4.2 ± 0.2] and UAS7 [27.8 ± 1.8]). Five patients (21.9%) did not display a recurrence of urticaria during a follow-up period (42.2 ± 10.1 weeks). In particular, 3 patients maintained response during a long-term follow-up (104, 25, and 72 weeks, respectively).

Of 19 retreated patients, 14 concluded a second course of treatment and, except for 1, displayed a significant improvement of symptoms (UAS 4.1 ± 0.2 vs 0.8 ± 0.5, *P* < .0001; UAS7 28.1 ± 1.8 vs 2.1 ± 0.9, *P* < .0001). Of note, a greater proportion of patients (8 of 14, 57.1%), though not statistically significant, achieved a complete remission (UAS7 = 0) as compared with the first course of treatment (11 of 29, 37.9%). The mean time of response was slightly reduced in comparison with that observed during the first cycle of therapy (5.0 ± 1.3 vs 6.1 ± 1.4 weeks, *P* = NS). After the second course of treatment, a reduction in the proportion of relapsing patients was observed (7 of 13, 53.8%, vs 19 of 24, 79.1%; *P* = .14). All these 7 patients were retreated with a third cycle, and all of them displayed complete remission (Figure 1). Only mild and transient injection-site reactions occurred in a small proportion of patients (5 of 30, 16.6%). One patient contracted intestinal parasite infestation due to *Entameba histolytica* and *Blastocystis hominis*. After negativization of stool analysis, a second course of treatment was begun due to clinical relapse of urticaria with no recurrence of parasite infestation. During the courses of treatment, no antiomalizumab antibodies were detected.

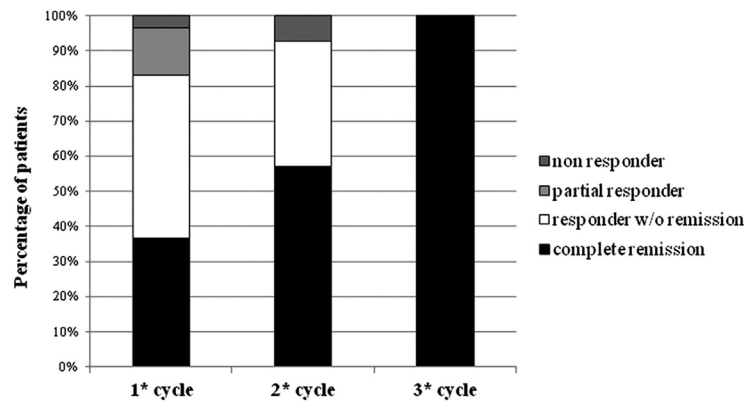


FIGURE 1. Clinical response to omalizumab over repeated cycles of treatment. Patients were classified at the end of each cycle of therapy as follows: responders if $UAS < 2$ and $UAS7 < 7$; nonresponders if UAS and $UAS7$ did not change significantly from the baseline values; partial responders if UAS was reduced in comparison with baseline, but $UAS \geq 2$ and $UAS7 \geq 7$; complete remission if UAS and $UAS7 = 0$. UAS , Urticaria activity score.

Our data, in agreement with other studies, confirm the efficacy of omalizumab in patients with CSU and different time of response as already demonstrated.^{3,4} We have identified patients who respond quickly (early responders) and those who require further administrations of the drug (late responders).⁵ The downregulation of FcεRI on effector cells has been described, also at skin level, as one of the mechanisms of action of omalizumab.^{6,7} However, this phenomenon requires several weeks. The rapid remission of urticaria by omalizumab is due to its ability to also induce the detachment of IgE from FcεRI.⁸ It could also be attributed to an interference with the cells' releasability, which is increased in patients with CSU.⁹ Considering that efficacy was observed in more than 80% of our patients, we cannot identify clinical markers of response to treatment.

The transitory nature of the response to omalizumab is underlined in our study by the fact that after few weeks we observed a relapse of urticaria, a phenomenon likely due to the natural course of the disease, the re-expression of IgE receptors, or the rebalancing of the intracellular pathways modified by the drug. However, we observed that a proportion of patients remained asymptomatic after drug interruption, hypothesizing that omalizumab had exerted a disease-modifying effect. Accordingly, what appears to hold greater interest is that the proportion of our patients who relapsed decreased in later courses of treatment. Notably, the percentage of treated patients who achieved complete remission of urticaria progressively increased over subsequent treatments. Overall, these results may suggest that omalizumab can modify the history of the disease over repeated courses of treatment. We cannot rule out that this phenomenon could arise if treatment with omalizumab were not limited to 6 months. Our study shows that omalizumab has a very low immunogenicity even after repeated interruption of therapy.

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