

Omalizumab for severe chronic spontaneous urticaria: Real-life experiences of 280 patients



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investigating and treating Chronic Spontaneous
Urticaria (CSU)

Clinical Implications

- In severe chronic spontaneous urticaria, attempts at increasing omalizumab dosing intervals or stopping therapy typically failed, suggesting that continuous treatment is needed to maintain remission.

TO THE EDITOR:

Chronic spontaneous urticaria (CSU) is a debilitating disorder. Thus, well-defined therapeutic strategies are required to achieve a maximal remission and maintain quality of life. Half of all patients with severe CSU require high doses of antihistamines coupled with short courses of steroids.¹ Cyclosporine A (CsA) is well established for its beneficial effect. However, frequent side effects and the fear of malignancies in long-term users required the development of better and safer therapeutic options. The beneficial effect of omalizumab in CSU has been shown in phase II and III clinical studies.^{2,3} Best responses were recorded with 300 mg given every 4 weeks. Rapid onset of action was noticed after 3 to 7 days, but in most patients only after 4 to 6 weeks. Well-controlled CSU was noted in about 60% to 70% of treated patients, and the percentage of patients who failed therapy was about 15%.^{4,5} However, many issues remain unanswered, including the following: What is the usefulness of increasing the dose above 300 mg when it is not effective enough? The possibility of maintaining a beneficial outcome after an increase in dosing intervals? and What is the rate of long remissions when omalizumab is stopped? This retrospective multicenter study was designed to assess these issues in a large group of patients with severe, refractory CSU.

Two hundred eighty patients with severe CSU (190 women and 90 men; age, 21–68 years [mean $\pm$ 44 years]) in whom omalizumab was started were summarized retrospectively. In Israel, omalizumab is allowed only after 6 months of other therapies have failed. The response to therapy was followed using the urticaria activity score over a period of 7 days (UAS7; 0–42

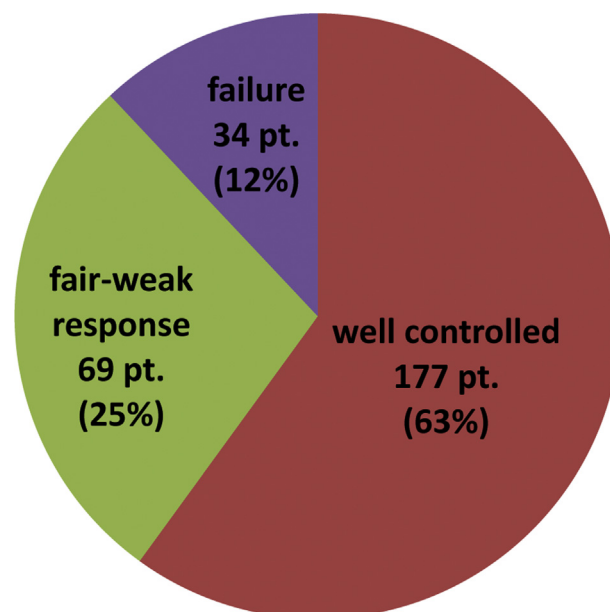


FIGURE 1. The percentage of well-controlled patients, fair-weak, and failures in all omalizumab-treated patients with CSU. *pt.*, Patient.

points), and was filled out by patients before and during the whole period of treatment. After 12 weeks of therapy, the response was defined as follows: When improvement was more than 80% from the baseline, it was considered well-controlled CSU; when improvement was 60% to 70%, it was considered a fair response; weak response, when improvement was 40% to 50%; and failure, when less than 30%. The decisions regarding increased doses, increase in dose intervals, or the possibility of stopping treatment were recorded.

The duration of CSU before starting omalizumab ranged between 10 months and 10 years (mean, 4.9 ± 1.4 years) and the mean UAS7 was 27.12 ± 6.7 points. Serious side effects were not identified; mild side effects were recorded in 10% of patients. As shown in Figure 1, well-controlled response was recorded in 63% of treated patients, in 25% there was a fair-weak response, and in 12% therapy failed. In well-controlled CSU, remission was maintained throughout the entire period of follow-up. The fair responders continued to only be on antihistamines, whereas the weak responders required the addition of short courses of steroids. After 3 months, when response to therapy was still weak, the dosage of omalizumab was increased. In 67% of them a further beneficial effect was noted (see Figure 2, A). It is interesting to note that in well-controlled patients the duration of urticaria ranged between 6 and 18 months and the UAS7 was 12 to 18 points. The weak responders and failures suffered from long-lasting urticaria of 24 to 60 months and had a UAS7 of 20 to 32 points. In well-controlled patients, a fast response was seen after 3 to 7 days of the first injection in 35.7% of patients. In 53.6%, a beneficial response was achieved after 4 to 6 weeks, and in 10.7%, a response was identified only after 6 to 8 weeks. In

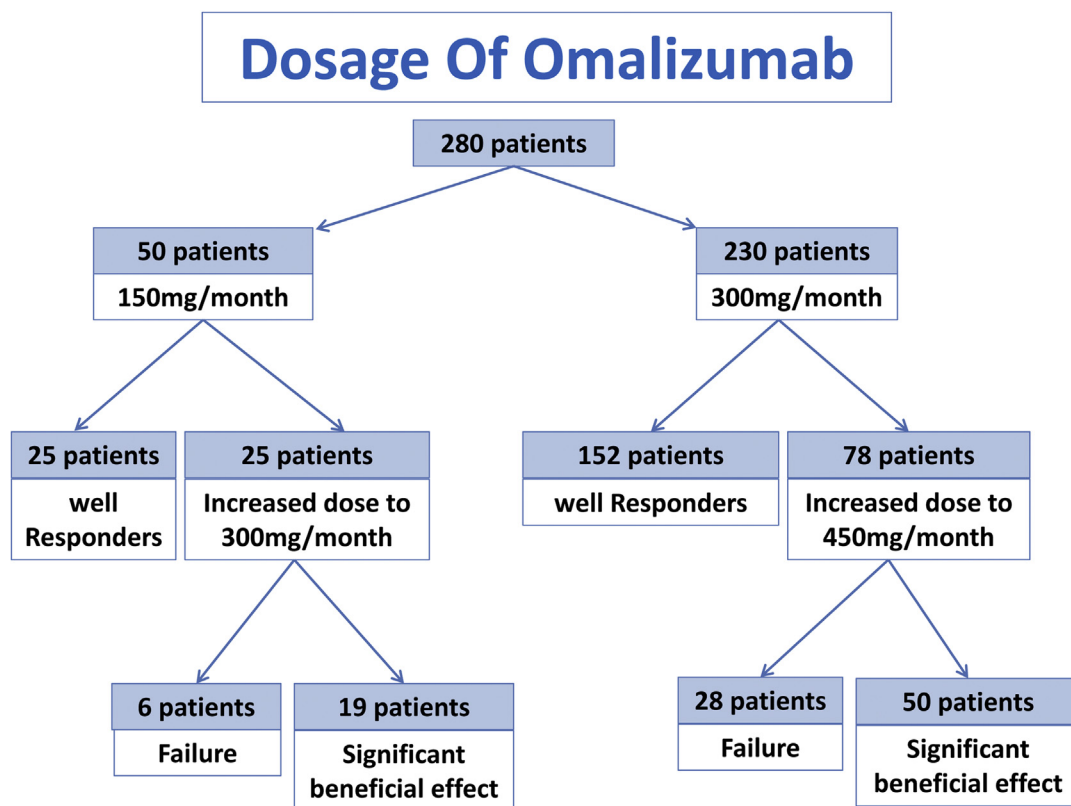
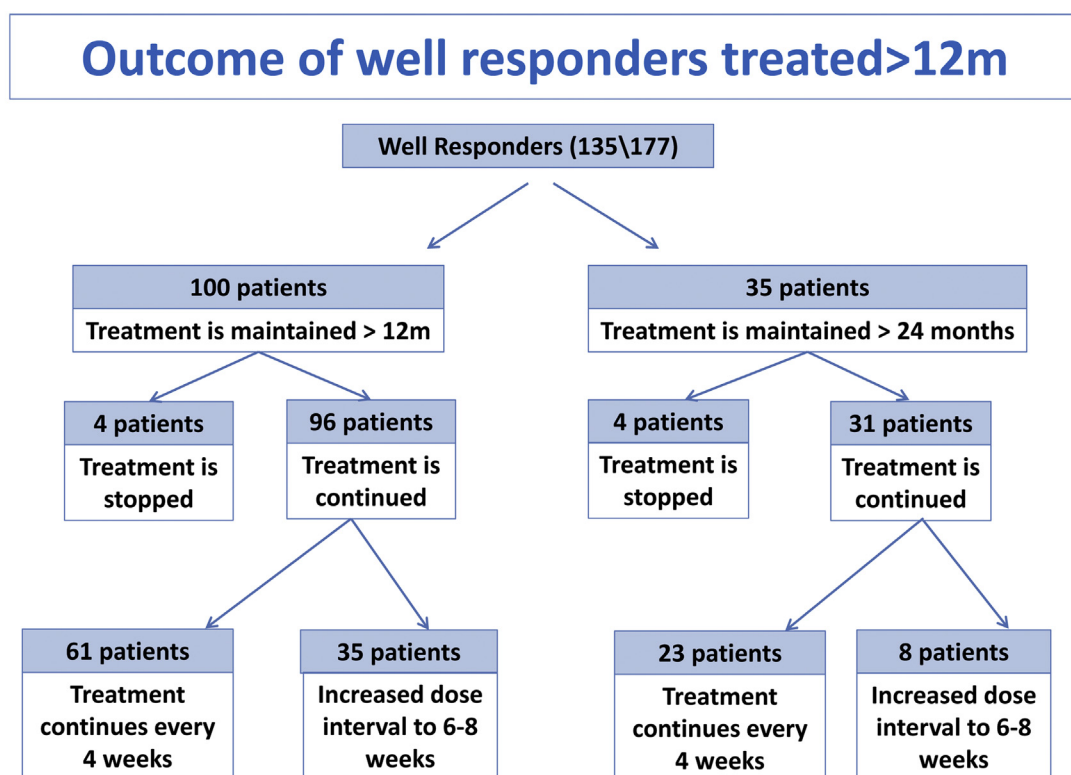
A**B**

FIGURE 2. **A,** A flowchart of the doses of omalizumab given to all patients with CSU. **B,** A flowchart of the clinical outcome including the possibility of increasing dose intervals between treatments or stopping the treatment altogether.

fair responders, a convincing response was recorded only after 8 to 10 weeks, achieving a plateau after 4 to 5 months. Here also, in later responders, urticaria was of a longer duration before the initiation of omalizumab than in fast responders. The outcome for well-controlled patients who were treated for more than 12 months is presented in Figure 2, B. Increase in the dose intervals was possible in only a few patients. All others were well maintained on 300 mg every 4 weeks. Only 8 patients were able to stop therapy and remained in full remission after 6 months. These were milder cases and of a shorter disease duration.

The success of omalizumab in treating severe CSU was a huge breakthrough, and the drug was quickly licensed by the Food and Drug Administration. In CSU, mast cell degranulation develops through 2 major pathways. The first involves highly cytotoxic monomeric IgEs, which by binding Fc region of immunoglobulin E receptor I (FcεRI) in the absence of antigens induce mast cell activation and histamine release.⁶ The second is the binding of autoreactive antibodies on activated skin mast cells. Thus, we suggest that the fast onset of response to omalizumab could be explained by the rapid sequestration of monomeric-free IgEs and the silencing of mast cell degranulation. The fast response could also be explained by the prevention of IgE binding to FcεRI on basophils and their notable reduction by day 8.^{7,8} The continuous binding of IgE autoantibodies against autoantigens such as thyroid peroxidase in late responders could gradually downregulate FcεRI expression on mast cells and contribute to their silencing.⁹

The severity of CSU and its duration before the administration of omalizumab may affect the therapeutic outcome. In our large survey, we could rarely stop omalizumab even after 1 or 2 years. The possible explanation for this is that these patients' illness was extremely severe. Another yet unresolved issue is the idea that increasing intervals between injections was possible in most patients. In our study, however, this was possible only in a few cases, thereby supporting the theory that in severe and long-lasting CSU, omalizumab is needed long-term. In severe CSU, one should consider the early initiation of omalizumab in the hope of achieving a better degranulation threshold. When increased doses of omalizumab from 150 to 300 mg are still insufficient, a further increase to 450 mg should be considered. Further studies are needed to assess outcome after 2 years.

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