

Omalizumab for Chronic Urticaria

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Chronic idiopathic urticaria (CIU)—chronic spontaneous urticaria (CSU) is defined as hives and/or angioedema that occurs daily, or almost daily, for >6 weeks independent of external stimuli.^{1,2} CIU has significant detrimental effects on quality of life.³ H1 antihistamines are the only approved treatment in CIU,² but more than 50% of patients are unresponsive to licensed doses of H1 antihistamines.¹ Add-on treatments (all unapproved by the US Food and Drug Administration) include leukotriene receptor antagonists, systemic steroids, cyclosporine, and methotrexates, but the data to support their use are not of high quality.⁴ Therefore, there is a need for new, efficacious, and well-tolerated treatments for patients with H1 antihistamine refractory CIU. Maurer et al⁵ recently reported results from 1 of the 3 phase III anti-IgE mAb omalizumab studies (Asteria-II) for treatment of CIU. They evaluated the efficacy and safety of omalizumab compared with placebo in 323 patients, 12 to 75 years of age, with moderate-to-severe refractory CIU despite receiving concomitant licensed doses of H1 antihistamine therapy.

This was a global, multicenter, 1:1:1:1 randomized, double-blind, placebo-controlled trial that compared 3 subcutaneous injections, separated by 4 weeks, of omalizumab at doses of 75 mg, 150 mg, or 300 mg, or placebo, followed by a 16-week observation period. The primary end point was the change from baseline in weekly itch severity score (ISS) at week 12. Major secondary end points included a change from baseline in a weekly number of hives score, the proportion of patients with a weekly urticaria activity score (UAS7, a composite score of the weekly ISS and weekly number of hives score [scale 0–42]) ≤ 6 , change from baseline in overall Dermatology Life Quality Index (DLQI), and the proportion of angioedema-free days from week 4 to week 12. Key inclusion criteria were a CIU diagnosis for ≥ 6 months, the presence of itch and hives for ≥ 8 consecutive weeks at any time before enrollment despite the current use of H1 antihistamine treatment, weekly UAS7 score ≥ 16 , and itch component of UAS7 ≥ 8 (scale 0–21) during 7 days before randomization (week 0). Key exclusion criteria were clearly defined underlying etiology for chronic urticaria (cold, physical,

etc), and routine doses within 30 days before enrollment of systemic steroids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, intravenous immunoglobulin, or other immunomodulators.

No major imbalances were observed between treatment groups for any of the patient baseline demographic or disease characteristics.⁵ The baseline data characterized a moderate-to-severe CIU-CSU patient population with baseline weekly ISS and UAS7 scores of 14 and 31, respectively. The patient population was predominantly approximately 40 years of age and women, with a high body mass index. A high incidence of angioedema also was seen (approximately 40%). The characteristics of the patient population in this study were generally representative of patients seen in clinical practice.

...These studies suggest that omalizumab will be a good therapeutic option for patients with CIU who do not respond to either licensed or higher doses of H1 antihistamines.

Maurer et al⁵ reported that, at week 12, the mean (SD) change from baseline in weekly ISS (primary end point) with placebo was -5.1 ± 5.6 ; with 75 mg of omalizumab, -5.9 ± 6.5 , $P = .46$; with 150 mg of omalizumab, -8.1 ± 6.4 , $P = .001$; and with 300 mg omalizumab, -9.8 ± 6.0 , $P < .001$. The reductions from baseline in mean weekly ISS were dose-dependent. Interestingly, omalizumab had an onset of effect on weekly ISS within a week in the 300-mg treatment arm and within 2 weeks in the 150-mg treatment arm. After the 12-week treatment period, the level of disease activity returned to the placebo level 8 and 12 weeks later for the lower (150 mg) and highest dose of omalizumab, respectively. Analysis of these data suggests that a 12-week treatment course, although effective, did not permanently affect the disease activity. How long one would need to be treated with omalizumab to see either a prolonged remission or “cure” remains to be determined and was not addressed in this study. All prespecified secondary end points also were statistically significantly different with omalizumab 150 mg (except for the angioedema-free days from weeks 4 to 12) and 300 mg compared with placebo. The observed treatment effects occurred in a dose-responsive fashion.

In the *post hoc* analyses, the proportion of patients who were completely hive-free, and who were itch- and hive-free (UAS7 = 0) at week 12 was 53.2% and 44.3%, respectively, in the omalizumab 300-mg group. Overall, analysis of the data suggests that three 300-mg doses of omalizumab induced complete remission (at least, of 12-week duration) in approximately half of the treated patients and induced good control (UAS7 < 6) in

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approximately two-thirds of patients at 12 weeks. Adverse event frequency was similar across groups. Compared with the known safety profile of omalizumab in the allergic asthma patient population, no new safety issues or concerns were identified.

Although these data support the use of omalizumab in patients with CIU who were unresponsive to licensed doses of H1 antihistamine therapy, clinicians often use higher than licensed doses of H1 antihistamines for this patient population. In a study by Kaplan et al,⁶ the safety and efficacy of 24 weeks of treatment with omalizumab in patients with persistent CIU-CSU despite treatment with H1 antihistamines at up to 4 times the approved dose plus H2 antihistamines, leukotriene receptor antagonists, or both, were evaluated. At week 12, the mean change from baseline in weekly ISS was -8.6 (95% CI, -9.3 to -7.8) in the omalizumab group compared with -4.0 (95% CI, -5.3 to -2.7) in the placebo group ($P < .001$). Significant improvements were seen for additional efficacy end points at week 12, and these benefits were sustained to week 24.

When taken together, these studies suggest that omalizumab will be a good therapeutic option for patients with CIU who do not respond to either licensed or higher doses of H1 antihistamines. Because this includes approximately 50% of patients with this disease, omalizumab could represent an exciting new

therapeutic option. Future work needs to define the exact placement of this option for CIU, the duration of treatment needed to effect a cure or prolonged remission, and how it works. Indeed, the mechanisms that lead to a therapeutic effect within 1 week were not specifically addressed in either study, but analysis of previous data suggests that it takes longer to significantly decrease the expression of the high affinity IgE receptors on either basophils (2 weeks)⁷ or mast cells (10 weeks).⁸

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