A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H_1-antihistamine–refractory chronic idiopathic urticaria

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Background: Proof-of-concept studies with omalizumab in patients with chronic idiopathic urticaria (CIU) have shown significant decreases in mean urticaria activity scores (UASs).
Objective: We sought to evaluate the efficacy and safety of omalizumab in patients with CIU who remain symptomatic despite concomitant H_1-antihistamine therapy.
Methods: This phase II, prospective, double-blind, placebo-controlled, dose-ranging study investigated omalizumab in patients aged 12 to 75 years in the United States and 18 to 75 years in Germany with a UAS over 7 days (UAS7) of 12 or greater despite antihistamine therapy. Patients were randomized 1:1:1:1 to receive a single subcutaneous dose of 75, 300, or 600 mg of omalizumab or placebo added to a stable dose of H_1-antihistamine. The primary efficacy outcome was change from baseline to week 4 in UAS7. Patients were followed for an additional 12 weeks to monitor safety.
Results: Ninety patients from the United States or Germany were enrolled. Both the 300-mg omalizumab group (−19.9 vs −6.9, $P < .001$) and the 600-mg omalizumab group (−14.6 vs −6.9, $P = .047$) showed greater improvement versus the placebo group in UAS7. No meaningful difference was observed for the 75-mg omalizumab group. Similar results were seen for key secondary end points of weekly hive and itch scores. Onset of effect occurred after 1 to 2 weeks. Omalizumab was well tolerated, and the incidence of adverse events was similar across treatment groups.
Conclusion: This study demonstrated that a fixed dose of 300 or 600 mg of omalizumab provides rapid and effective treatment of CIU in patients who are symptomatic despite treatment with H_1-antihistamines. (J Allergy Clin Immunol 2011;128:567-73.)

Key words: *Chronic idiopathic urticaria, chronic spontaneous urticaria, H_1-antihistamine, hive, itch, omalizumab, urticaria activity score, dose ranging*

Urticaria with a nonspecific cause characterized by the spontaneous emergence of wheals, angioedema, or both without external physical stimuli is classified as chronic idiopathic urticaria (CIU) in the United States or chronic spontaneous urticaria in Europe if symptoms occur daily or almost daily for more than 6 weeks.[1,2] CIU has a significant effect on patients' quality of life both physically and psychologically, with loss of energy, social isolation, and emotional distress similar to that seen in patients awaiting coronary artery bypass surgery.[3,4]

In approximately half of the patients with CIU, no cause for the condition has been identified[2,5]; however, approximately 30% to 50% of patients with CIU reportedly produce IgG autoantibodies against either IgE or its high-affinity receptor (FcεRI).[5] Cross-linking autoantibodies directed against the α-subunit of FcεRI lead to histamine release through degranulation of cutaneous mast cells and blood basophils.[6,7] A subgroup of patients who exhibit IgE autoantibodies against thyroperoxidase has also recently been identified. Although autoantibodies are considered to play a role in the cause of certain subtypes of CIU, autoantibodies have also been found in patients without CIU, and their clinical significance remains unclear.[8-10]

Current guidelines for the treatment of CIU recommend a stepwise approach beginning with nonsedating H_1-antihistamines (nsAHs)[11] and then increasing the dose of nsAH up to 4-fold if symptoms persist before changing to a different nsAH or adding a leukotriene antagonist.[11,12] If symptoms do not abate with any of these interventions, the guidelines recommend adding cyclosporin A, an H_2-antihistamine, dapsone, or omalizumab. Cyclosporine has been shown to be effective when administered with an nsAH,[13] but concerns about potential toxicities preclude it from being recommended as standard treatment.[11] Data on the combination of H_1- and H_2-antihistimines is favorable but

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Abbreviations used
AE: Adverse event
CIU: Chronic idiopathic urticaria
nsAH: Nonsedating H1-antihistamine
UAS: Urticaria activity score
UAS7: Urticaria activity score over 7 days

limited, and dapsone has only been tested in uncontrolled clinical trials.[11] Exacerbations are treated with systemic steroids for 3 to 7 days, but longer-term exposure is not recommended because of unavoidable severe adverse events (AEs).[11]

Omalizumab is a recombinant mAb that is approved for the treatment of moderate-to-severe persistent asthma in patients with a positive skin test response or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (in the United States) or inhaled corticosteroids plus a long-acting inhaled β_2-agonist (in Europe).[14,15] Omalizumab blocks the binding of IgE to the FcεRI receptor on the surface of target cells, including mast cells and basophils, thus reducing receptor expression[16,17] and the release of inflammatory mediators.[18]

After initial case reports of beneficial effects of omalizumab in patients with chronic urticaria,[19,20] 2 proof-of-concept trials investigated omalizumab in patients with active CIU who remained symptomatic despite antihistamine therapy.[21,22] Both of these trials used the US Food and Drug Administration–approved dosing table for asthma, determining the omalizumab dose based on body weight and screening IgE levels.[14] In each of these studies, omalizumab improved mean urticaria activity scores (UASs) as early as week 2, and scores continued to improve through week 16.[21,22] Subsequently, additional case studies have reported beneficial effects for omalizumab in patients with recalcitrant urticaria.[23,24]

The purpose of the present study was to evaluate the efficacy and safety of omalizumab in patients with CIU who remained symptomatic despite treatment with H_1-antihistamines. Because the mechanism of action for omalizumab in patients with CIU might not be directly linked to IgE reduction, the study was additionally designed to determine the optimal dose of omalizumab for the treatment of CIU.[21,22]

METHODS

MYSTIQUE was a phase II, prospective, multicenter, international (United States and Germany), randomized, double-blind, placebo-controlled, dose-ranging study of a single subcutaneous dose of omalizumab in patients with CIU refractory to H_1-antihistamines (see Table E1 in this article's Online Repository at www.jacionline.org). Patients were enrolled at 26 study centers in the United States and Germany, which included academic institutions, allergy offices, and research/clinical groups. This study was conducted in accordance with US Food and Drug Administration regulations, the International Conference on Harmonization the E6 Guideline for Good Clinical Practice, and applicable local, state, and federal laws in the United States and Germany. All sites obtained institutional review board approval to conduct this study and obtained written informed consent from study participants before enrolment.

Study population

The study included patients aged 12 to 75 years (in the United States) or 18 to 75 years (in Germany) with a history of CIU (>3 months) without a clearly defined cause. At the time of screening, eligible patients had moderate-to-severe CIU (pruritus and hives for >3 days in a 7-day period for >6 consecutive weeks) despite treatment with an approved dose of an H_1-antihistamine. Allowable antihistamines were 10 mg of cetirizine once daily, 5 mg of levocetirizine dihydrochloride once daily, 60 mg of fexofenadine twice per day or 180 mg once daily, 10 mg of loratadine once daily, or 5 mg of desloratadine once daily.

Patients were required to have a daily UAS of 4 or more established in the clinic, and a diary-based UAS over 7 days (UAS7) of 12 or more during the run-in period before randomization (day 0) despite stable doses of H_1-antihistamine. The daily UAS is a composite score (scale, 0-6) calculated as the sum of the daily average morning and evening scores for severity of itch (0, none; 1, mild; 2, moderate; and 3, severe) and number of hives (0, none; 1, 1-6 hives; 2, 7-12 hives; and 3, >12 hives).[25-27]

Exclusion criteria included weight less than 40 kg, pregnancy or lactation, any other skin disease associated with pruritus, treatment with omalizumab within 12 months before screening, contraindication to diphenhydramine, treatment with any investigational agent within 30 days of screening, any clinically relevant major systemic disease that could potentially complicate interpretation of study results, and inability to comply with study and follow-up procedures. Patients were not permitted regular use (daily/every other day) of any of the following medications/treatments from the indicated time period before the screening visit throughout the end of the treatment period: 3 months prior—hydroxychloroquine, sulfasalazine, dapsone, methotrexate, cyclophosphamide, intravenous immunoglobulin, plasmapheresis, or other mAb therapies; 6 weeks prior—doxepin; 1 month prior—cyclosporine; and 1 week prior—H_2-antihistamines and leukotriene receptor antagonists. Use of systemic corticosteroids or cutaneous corticosteroids was not allowed during the screening, run-in, or treatment phases; however, intranasal, inhaled, and ophthalmic steroids were permitted.

Study design

The study consisted of 4 phases (Fig 1): screening (week −2 to week −1), run-in (week −1 to day 0), treatment (day 0 through week 4), and follow-up (week 4 through week 16). A patient's eligibility to enter the trial was determined at the screening visit. During the run-in period, patients established baseline symptom scores in their diaries; those with a UAS7 of 12 or more were eligible for randomization. At day 0, patients were randomized in a 1:1:1:1 ratio to receive a single dose of 75, 300, or 600 mg of omalizumab or placebo. Randomization was performed by using a dynamic randomization scheme stratified by weight (<80 kg and ≥80 kg) and administered through an interactive voice-response system. Patients, all study personnel, the designated evaluating physician, and the sponsor and its agents (with the exception of the interactive voice-response system service provider) were blinded to treatment assignment. After completing the 4-week treatment period, patients were followed for an additional 12 weeks to collect safety data. From screening through week 4, all patients were provided 25 mg of diphenhydramine to use as a rescue medication for pruritus relief on an as-needed basis. The maximum allowable daily dose of diphenhydramine was 75 mg in the United States and 50 mg in Germany. Patients who required any other medications (including systemic corticosteroids) to treat persistent/worsening disease were discontinued from the study.

Study end points

Because frequent variation in disease intensity during the course of a day is common, the assessment of disease activity was based on a weekly aggregate UAS score (UAS7). The UAS7 is the sum of the daily average UAS scores (average of morning and evening scores) over 7 days (scale, 0-42).[26,27] The primary efficacy outcome was the change in UAS7 from baseline to the end of the treatment period (week 4).

Key secondary efficacy outcomes included the change in weekly pruritus score and weekly score for the number of hives from baseline to week 4 in the treatment period. The pruritus score was measured twice daily (morning and evening) on a scale of 0 (none) to 3 (intense). The weekly pruritus score was the sum of daily average (over morning and evening) pruritus scores over 7 days (range, 0-21). Similarly, the number of hives was measured twice daily (morning and evening) on a scale of 0 (none) to 3 (>12 hives). The weekly