Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy

Allen Kaplan, MD,[a] Dennis Ledford, MD,[b] Mark Ashby, PhD,[c] Janice Canvin, MD, FRCPC,[d] James L. Zazzali, PhD,[c] Edward Conner, MD,[c] Joachim Veith, MD,[c] Nikhil Kamath, MD,[e] Petra Staubach, MD,[f] Thilo Jakob, MD,[g] Robert G. Stirling, MB, FRACP,[h] Piotr Kuna, MD, PhD,[i] William Berger, MD,[j] Marcus Maurer, MD,[k] and Karin Rosén, MD, PhD[c] *Charleston, SC, Tampa, Fla, South San Francisco and Mission Viejo, Calif, Horsham and Welwyn Garden City, United Kingdom, Mainz, Freiburg, and Berlin, Germany, Melbourne, Australia, and Lodz, Poland*

Background: Patients with chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU) often continue to experience symptoms despite receiving standard-of-care therapy with H_1-antihistamines along with 1 or more add-on therapies.

Objectives: We sought to evaluate the safety and efficacy of 24 weeks of treatment with omalizumab in patients with persistent CIU/CSU despite treatment with H_1-antihistamines at up to 4 times the approved dose plus H_2-antihistamines, leukotriene receptor antagonists, or both.

Methods: In this phase III study patients were randomized to receive 6 subcutaneous injections at 4-week intervals of either 300 mg of omalizumab or placebo, followed by a 16-week observation period. The primary objective of the study was to evaluate the overall safety of omalizumab compared with placebo. Efficacy (itch severity, hive, and urticaria activity scores) was evaluated at weeks 12 and 24.

Results: The overall incidence and severity of adverse events and serious adverse events were similar between omalizumab and placebo recipients; the safety profile was consistent with omalizumab in patients with allergic asthma. At week 12, the mean change from baseline in weekly itch severity score 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; these benefits were sustained to week 24.

Conclusion: Omalizumab was well tolerated and reduced the signs and symptoms of CIU/CSU in patients who remained symptomatic despite the use of H_1-antihistamines (up to 4 times the approved dose) plus H_2-antihistamines, leukotriene receptor antagonists, or both. (J Allergy Clin Immunol 2013;132:101-9.)

Key words: *Chronic idiopathic urticaria, chronic spontaneous urticaria, H_1-antihistamine, H_2-antihistamines, hive, itch, leukotriene receptor antagonist, omalizumab, pruritus, wheal*

Chronic idiopathic urticaria (CIU), also referred to as chronic spontaneous urticaria (CSU) in recent guidelines adopted by European and global allergy and dermatology associations, is characterized by itchy hives that occur for at least 6 weeks with or without angioedema but have no apparent trigger (eg, allergen, physical event, and drugs). The mainstay of treatment for patients with CIU/CSU is nonsedating H_1-antihistamine therapy.[1] However, in a significant proportion of patients, symptoms persist

From [a]the Medical University of South Carolina, Charleston; [b]Morsani College of Medicine and James A. Haley VA Hospital, University of South Florida, Tampa; [c]Genentech, Inc, South San Francisco; [d]Novartis Pharmaceuticals UK Ltd, Horsham; [e]Roche Products Ltd, Welwyn Garden City; [f]the Department of Dermatology, University Medical Center Mainz; [g]the Allergy Research Group, University Medical Center Freiburg; [h]Allergy Immunology and Respiratory Medicine, Alfred Health, Monash University, Melbourne; [i]the Medical University of Lodz; [j]Allergy and Asthma Associates, Mission Viejo; and [k]the Department of Dermatology and Allergy, Charité-Universitätsmedizin, Berlin.

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Corresponding author: Karin Rosén, MD, PhD, Genentech, Inc, 1 DNA Way, South San Francisco, CA 94080-4990. E-mail: rosen.karin@gene.com.

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Abbreviations used

AE: Adverse event
CIU/CSU: Chronic idiopathic urticaria/chronic spontaneous urticaria
CU-Q_2oL: Chronic Urticaria Quality-of-Life Questionnaire
DLQI: Dermatology Life Quality Index
eDiary: Electronic diary
ISS: Itch severity score
LSM: Least squares mean
LTRA: Leukotriene receptor antagonist
MID: Minimally important difference
UAS: Urticaria activity score
UAS7: Urticaria activity score over 7 days

despite treatment with H_1-antihistamines, even when administered at up to 4 times the approved dose.[2-4] Should updosing of H_1-antihistamines prove unsuccessful as second-line therapy, current European and global guidelines describe several alternative add-on therapies as third-line treatment options, including leukotriene receptor antagonists (LTRAs), cyclosporine, dapsone, H_2-antihistamines, omalizumab, and methotrexate.[1] Cyclosporine is effective but has the potential for severe side effects, necessitating monitoring of blood pressure and renal function. Most of the remaining alternatives are based on low-quality clinical evidence. Oral corticosteroids can be used to treat CIU/CSU exacerbations, and their use is sometimes unavoidable, but they are not recommended as a long-term treatment option given the potential for severe side effects associated with chronic use.[1]

Omalizumab is a humanized anti-IgE mAb approved for the treatment of inadequately controlled moderate-to-severe (United States) or severe (Europe) allergic asthma.[5,6] Initial studies suggested that omalizumab improved hives or wheals and pruritus in patients with CIU/CSU refractory to H_1-antihistamines.[7,8] These findings were supported by a phase II study (MYSTIQUE), which included 90 patients with CIU/CSU,[9] and an additional study involving a subgroup of patients with CIU/CSU (n = 49) with IgE antibodies against thyroperoxidase (X-QUISITE).[10] Omalizumab demonstrated rapid and beneficial effects on the signs and symptoms of CIU/CSU in both studies.

Subsequently, a randomized, double-blind placebo-controlled trial (Q4882g; Asteria-II; Clinicaltrials.gov identifier: NCT01292473) involving 323 patients was conducted as part of a series of phase III studies designed to assess the efficacy and tolerability of subcutaneous omalizumab in patients aged 12 to 75 years with CIU/CSU.[11] Patients with moderate-to-severe CIU/CSU who remained symptomatic despite receiving a licensed or approved dose of a second-generation H_1-antihistamine had significant improvement in their symptoms when treated with 150 or 300 mg of omalizumab over 12 weeks (dosing at 4-week intervals) compared with placebo. Efficacy was dose dependent, with the greatest effects seen with the 300-mg dose. No new safety issues or concerns were identified compared with the known safety profile of omalizumab in the allergic asthmatic patient population.

The primary objective of the current study was to assess the safety of omalizumab compared with placebo over 24 weeks when administered as an add-on therapy in patients with CIU/CSU whose signs and symptoms persisted despite treatment with H_1-antihistamines (including up to 4 times the approved dose) plus H_2-antihistamines, LTRAs, or both. The efficacy of omalizumab compared with that of placebo was also assessed.

METHODS

Study design

This global phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study investigated the safety, tolerability, and efficacy of 300 mg of omalizumab in patients aged 12 to 75 years (18-75 years in Germany) with CIU/CSU who remained symptomatic despite treatment with H_1-antihistamines at up to 4 times the approved dose plus H_2-antihistamines, LTRAs, or both. The study involved a 2-week screening period, a 24-week treatment period, and a 16-week follow-up period (during which omalizumab was not administered). Patients from 65 centers were randomized in a 3:1 ratio to receive subcutaneous injections of either omalizumab (n = 252) or placebo (n = 84) at intervals of 4 weeks for a total of 24 weeks (6 doses). Randomization was stratified according to baseline weekly itch severity score (ISS), baseline weight, and study site (see the Methods section in this article's Online Repository at www.jacionline.org for further details on the randomization process). Throughout the treatment period, participants were required to maintain stable doses of their prerandomization combination therapy with H_1-antihistamine treatment plus H_2-antihistamines, LTRAs, or both. For the duration of the study, patients were provided with 25 mg of diphenhydramine as rescue medication for symptom relief (up to a maximum of 3 doses per 24-hour period or fewer depending on local regulations).

The study protocol was approved by the institutional review board or ethics committee at each center, and the study was conducted in accordance with US Food and Drug Administration regulations, the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and any other applicable national laws. An independent data-monitoring committee monitored the study conduct and reviewed blinded and unblinded safety data every 6 months for the duration of the study.

Study population

Patients were eligible for inclusion if they met the following criteria: 12 to 75 years old (18-75 years old in Germany); CIU/CSU for 6 months or longer; itch and hives for more than 6 consecutive weeks before enrollment despite therapy with H_1-antihistamines plus H_2-antihistamines, LTRAs, or both; an urticaria activity score (UAS) over 7 days (UAS7) of 16 or greater (on a scale ranging from 0-42, with higher scores indicating greater activity)[12] and a weekly ISS of 8 or greater (range, 0-21) during 7 days before randomization obtained from a daily symptom electronic diary (eDiary) completed by the patient[13,14]; an in-clinic physician-assessed UAS (range, 0-6) of 4 or greater on one of the screening visit days (days −14, −7, or 1); treatment with a regimen that included an H_1-antihistamine (up to 4 times the approved dosage) plus H_2-antihistamines, LTRAs, or both H_2-antihistamines and LTRAs for CIU/CSU for 3 or more consecutive days immediately before day −14; willingness and ability to complete a daily symptom eDiary throughout the study; and no missing eDiary entries in the 7 days before randomization.

Key exclusion criteria comprised the following: a clearly defined underlying cause for chronic urticaria (eg, physical urticaria); doses administered daily or every other day for 5 or more consecutive days of systemic or topical corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or intravenous immunoglobulin within 30 days before day −14; history of malignancy; hypersensitivity to omalizumab; treatment with omalizumab within the previous year; evidence of parasitic infection; history of anaphylactic shock; or women who are pregnant, breast-feeding, or of childbearing potential and not using acceptable contraception.

Written informed consent was obtained from each participant or the participant's parent or legal guardian (if participant was <18 years of age) before they were included in the study.

Assessments

Each patient completed the Urticaria Patient Daily Diary[13,14] by using an eDiary for the duration of the study, recording ISSs (0, none; 1, mild; 2, moderate; and 3, severe), number of hives (0, none; 1, 1-6 hives; 2, 7-12 hives; and 3, >12 hives), and size of the largest hive (0, none; 1, <1.25 cm; 2, 1.25-2.5 cm; and 3, >2.5 cm) twice daily; sleep and daily activity interference