Casale et al. World Allergy Organization Journal (2024) 17:100943
http://doi.org/10.1016/j.waojou.2024.100943

WORLD ALLERGY ORGANIZATION JOURNAL

BRIEF RESEARCH REPORT

Open Access

Does angioedema in patients with chronic spontaneous urticaria impact response to omalizumab?

Thomas B. Casale, MD[a]*, Benjamin Trzaskoma, MS[b], Michael Holden, MD[b], Jonathan A. Bernstein, MD[c] and Marcus Maurer, MD[d,e]

ABSTRACT

The presence of angioedema, or deep skin swelling, in addition to hives (wheals) in patients with chronic spontaneous urticaria (CSU) can complicate disease management. There is evidence that omalizumab is effective for patients with CSU with angioedema, but the time to a clinically meaningful response has not been assessed. This *post hoc* analysis examined data from the phase 3, randomized, double-blind ASTERIA I and ASTERIA II studies: patients with CSU with hives were grouped by presence (n = 216) or absence of angioedema (n = 265) at baseline. The time to minimally important difference (MID, change from baseline of ≥11 points) in weekly Urticaria Activity Score (UAS7) was analyzed using Kaplan-Meier analyses. Median time to MID for omalizumab 300 mg was similar in patients with and without angioedema. Median time to MID for omalizumab 150 mg was similar to 300 mg for patients without angioedema, and was longer for patients with angioedema. Therefore, the response to omalizumab for patients with CSU with angioedema was dose dependent. We recommend that the best approach for clinicians, in line with guidelines, would be initial administration of omalizumab 300 mg every 4 weeks for all patients.

Clinical trials registration: Clinicaltrials.gov NCT01287117 (registered 27 January 2011) and NCT01292473 (registered 7 February 2011).

Keywords: Angioedema, Chronic spontaneous urticaria, Omalizumab

INTRODUCTION

The presence of angioedema, or deep skin swelling, in addition to hives (wheals) in patients with chronic spontaneous urticaria (CSU) can complicate disease management. Angioedema is reported in approximately 50% of CSU cases (estimated 33%–67%[1] of patients with hives and 47.2% in pivotal trials[2]) and leads to more severe and prolonged disease.[1,2] Recent data from the international, observational, Chronic Urticaria Registry (CURE) found that patients with CSU with hives plus angioedema had high rates of psychiatric conditions, autoimmune disease, nonsteroidal anti-inflammatory drug

[a]Division of Allergy and Immunology, University of South Florida, Tampa, FL, USA
*Corresponding author. Division of Allergy and Immunology, Joy McCann Culverhouse Clinical Research Center, University of South Florida, 12901 Bruce B. Downs Blvd., MDC 19, Tampa, FL 33612, USA. E-mail: tbcasale@usf.edu
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2024.100943

Received 18 April 2024; Received in revised form 20 June 2024; Accepted 20 July 2024
Online publication date xxx

hypersensitivity, and systemic symptoms such as malaise, joint/bone/muscle pain, and poorer quality of life versus patients with either only hives or only angioedema.[3]

There is evidence that omalizumab, an anti-immunoglobulin E (IgE) antibody approved for the treatment of CSU (150 mg or 300 mg every 4 weeks, independent of serum IgE level or body weight) for patients who do not show benefit from a second-generation H1 antihistamine, is effective for patients with CSU with angioedema. For example, analysis of primary clinical trials showed that omalizumab (300 mg every 4 weeks) increased the proportion of angioedema-free days;[2] a clinical trial showed that add-on omalizumab (300 mg every 4 weeks) improved angioedema-related quality of life and skin-related quality of life;[4] and the CURE study showed that omalizumab (80% of patients on 300 mg every 4 weeks) led to a complete response in 67% of treated patients with hives plus angioedema.[3] However, the time to a clinically meaningful response to omalizumab for patients with CSU with angioedema has not been assessed.

METHODS

This *post hoc* analysis examined data from the phase 3, randomized, double-blind ASTERIA I (NCT01287117) and ASTERIA II (NCT01292473) studies, which enrolled patients ≥12 years of age with moderate-to-severe H1 antihistamine-refractory CSU.[5,6] For this analysis, patients with CSU with hives were grouped by presence or absence of angioedema at baseline. The time to minimally important difference (MID, change from baseline of ≥11 points[7]) in weekly Urticaria Activity Score (UAS7) was analyzed using Kaplan-Meier analyses. Safety results for ASTERIA I and ASTERIA II have been reported previously.[5,6]

RESULTS

At baseline, characteristics were similar between treatment groups regardless of the presence of angioedema (Table 1). Patients with angioedema had slightly lower IgE and UAS7 (Table 1) and worse quality of life (by the Dermatology Life Quality Index) than patients without angioedema (n = 216 versus 265; mean [standard deviation, SD] scores 14.7 [6.5] versus 11.9 [6.2]). Analyses of median time to MID in UAS7 indicated that

	Patients with Angioedema at Baseline			Patients with No Angioedema at Baseline		
	Placebo n = 74	Omalizumab 150 mg n = 76	Omalizumab 300 mg n = 66	Placebo n = 85	Omalizumab 150 mg n = 86	Omalizumab 300 mg n = 94
Age, mean (SD)	41.5 (14.4)	44.3 (13.4)	43.0 (12.9)	41.9 (14.1)	40.1 (13.5)	43.6 (13.8)
Female, n (%)	49 (66.2)	64 (84.2)	50 (75.8)	58 (68.2)	65 (75.6)	73 (77.7)
BMI, mean (SD)	29.1 (6.9)	29.3 (7.3)	29.6 (6.9)	29.5 (7.1)	30.4 (7.7)	28.9 (6.4)
Duration CSU (years), mean (SD)	6.6 (9.3)	8.4 (10.5)	6.9 (8.7)	7.5 (10.9)	6.6 (7.6)	5.6 (6.8)
Total IgE (IU/mL), median	67.0	68.5	58.5	92.5	73.5	103.5
UAS7, mean (SD)	32.4 (6.0)	31.1 (7.1)	31.2 (6.2)	29.9 (6.9)	30.6 (7.2)	29.9 (6.6)

Table 1. Baseline patient characteristics. *UAS7, weekly Urticaria Activity Score*

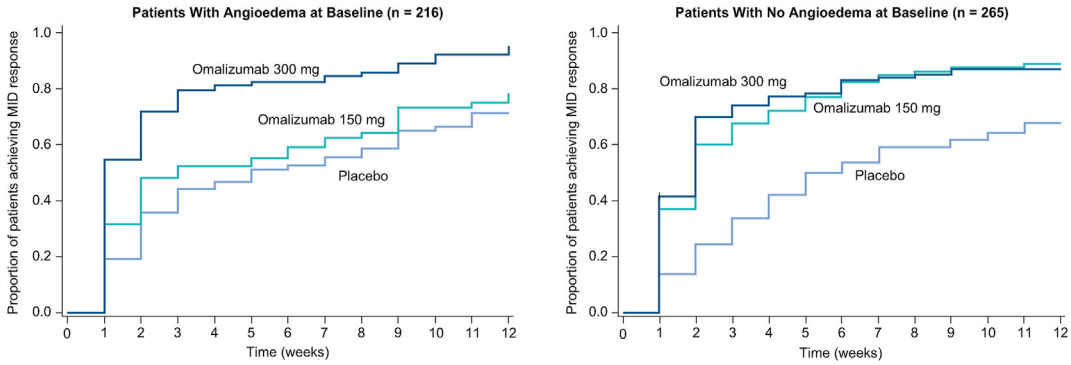

Fig. 1 Median time to minimally important difference (MID; change from baseline of ≥11 points) in weekly Urticaria Activity Score (UAS7) for patients with or without angioedema at baseline

omalizumab 300 mg had a similar effect, by median time to response and by pattern of response, in patients with and without angioedema (Fig. 1). For patients with angioedema, the median time to MID was 1.0 week for omalizumab 300 mg (5.0 weeks for placebo; hazard ratio 2.69; 95% confidence interval [95% CI] 1.80–4.02; log rank $P < 0.0001$ versus placebo); for patients without angioedema, the median time to MID was 2.0 weeks (5.0 weeks for placebo; hazard ratio 2.53; 95% CI 1.77–3.61; $P < 0.0001$ versus placebo). In contrast, omalizumab 150 mg was effective (by time to UAS7 response; statistically significant versus placebo) in patients without angioedema, but not in patients with angioedema, where it was similar to placebo (Fig. 1). For patients with angioedema, the median time to MID was 3.0 weeks for omalizumab 150 mg (5.0 weeks for placebo; hazard ratio 1.31; 95% CI 0.88–1.95; log rank $P = 0.2476$ versus placebo); for patients without angioedema, the median time to MID was 2.0 weeks (5.0 weeks for placebo; hazard ratio 2.30; 95% CI 1.61–3.27; $P < 0.0001$ versus placebo).

DISCUSSION

In summary, although our results are limited by the *post hoc* nature of this analysis, the response to omalizumab for patients with CSU with angioedema was dose-dependent: median time to clinically meaningful response was longer for patients on 150 mg versus 300 mg. However, given this particular comparison is indirect, this result should be interpreted with caution and clinicians should rely on their clinical judgement for interpretation of this finding.

In addition, in patients with angioedema, omalizumab 300 mg (but not 150 mg) was significantly different from placebo. This is in line with international guidelines, which recommend an initial omalizumab dose of 300 mg every 4 weeks for all patients with CSU (without consideration of angioedema status); however, a systematic review of real-world data found that about one-third of patients with CSU are initially prescribed 150 mg.[8] This is despite evidence that, although 150 mg omalizumab every 4 weeks was effective in ASTERIA I/II at Week 12 (with about 50% of patients with angioedema),[9] most patients (79.2%) in an open-label trial (about 60% with angioedema) who started on 150 mg were required to step up to 300 mg and few patients on 150 mg had sustained symptom control.[10] Given that angioedema, which affects about one-half of patients with CSU, can worsen the severity of CSU, each day that patient quality of life can be improved is important. Therefore, even though 150 mg every 4 weeks is an approved regimen available to physicians, we recommend the best approach for clinicians would be initial administration of omalizumab 300 mg every 4 weeks, especially as the clinical evidence for effectiveness at this dose for all patients is clear and consistent.

Abbreviations

CSU, chronic spontaneous urticaria; CURE, Chronic Urticaria Registry; IgE, immunoglobulin E; MID, minimally important difference; Q4W, every 4 weeks; UAS7, Urticaria Activity Score over 7 days.

Funding

The ASTERIA studies were funded by Genentech, Inc., a member of the Roche Group, and Novartis Pharma AG. This

analysis was funded by Genentech, Inc., a member of the Roche Group. Medical writing assistance was provided by Janelle Keys, PhD, of Envision Pharma Group, and funded by Genentech, Inc.

Data availability

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Author contributions

All authors conceived the study, interpreted the results, and prepared the manuscript. BT analyzed the data. All authors critically reviewed the manuscript and approved the final draft.

Ethics approval

Study protocols were approved by applicable institutional review boards and ethics committees before trial commencement, and all patients provided informed consent. Clinical trials registration: Clinicaltrials.gov NCT01287117 (registered 27 January 2011) and NCT01292473 (registered 7 February 2011).

Role of the sponsor

Genentech, Inc., was involved in the study design, the analysis of data, the preparation of the manuscript, and the decision to submit the manuscript for publication.

Declaration of competing interest

Thomas Casale is a consultant and speaker bureau member for Genentech, Inc.; consultant for Novartis Pharmaceuticals Corporation. Benjamin Trzaskoma and Michael Holden are employees of Genentech, Inc.; stockholders in Roche. Jonathan Bernstein is a consultant and PI for Genentech, Inc., Novartis, Amgen, GSK, Sanofi-Regeneron, AstraZeneca, Celldex, Allakos, Escient, Teva, Takeda/Shire, CSL Behring, Biocryst, Kalvista, Ionis, Biomarin, Pharming, Jasper. Marcus Maurer is a speaker and/or advisor for and/or has received research funding from Allakos, Alexion, Almirall, Alvotech, Amgen, Aquestive, Arcensus, argenX, AstraZeneca, Astria, BioCryst, Blueprint, Celldex, Celltrion, Clinuvel, Cogent, CSL Behring, Escient, Evommune, Excellergy, Genentech, GSK, Incyte, Jasper, Kashiv, Kalvista, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Mitsubishi Tanabe Pharma, Moxie, Noucor, Novartis, Orion Biotechnology, Pharvaris, Resonance Medicine, Sanofi/Regeneron, Santa Ana Bio, Septerna, Servier, Takeda, Teva, Third HarmonicBio, Valenza Bio, Vitalli Bio, Yuhan Corporation, Zurabio.

Author details

[a]Division of Allergy and Immunology, University of South Florida, Tampa, FL, USA. [b]Genentech, Inc., South San Francisco, CA, USA. [c]College of Medicine, University of Cincinnati, Cincinnati, OH, USA. [d]Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [e]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany.

REFERENCES

1. Sussman G, Abuzakouk M, Bérard F, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: analyses from ASSURE-CSU. *Allergy*. 2018;73:1724–1734.
2. Zazzali JL, Kaplan A, Maurer M, et al. Angioedema in the omalizumab chronic idiopathic/spontaneous urticaria pivotal studies. *Ann Allergy Asthma Immunol*. 2016;117:370–377.e1.
3. Buttgereit T, Vera C, Aulenbacher F, et al. Patients with chronic spontaneous urticaria who have wheals, angioedema, or both, differ demographically, clinically, and in response to treatment - results from CURE. *J Allergy Clin Immunol Pract*. 2023;11:3515–3525.e4.
4. Staubach P, Metz M, Chapman-Rothe N, et al. Effect of omalizumab on angioedema in H1-antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial. *Allergy*. 2016;71:1135–1144.
5. Maurer M, Rosén K, Hsieh HJ. Omalizumab for chronic urticaria. *N Engl J Med*. 2013;368:2530.
6. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol*. 2015;135:925.
7. Mathias SD, Crosby RD, Zazzali JL, Maurer M, Saini SS. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2012;108:20–24.
8. Bernstein JA, Kavati A, Tharp MD, et al. Effectiveness of omalizumab in adolescent and adult patients with chronic idiopathic/spontaneous urticaria: a systematic review of 'real-world' evidence. *Expet Opin Biol Ther*. 2018;18:425–448.
9. Casale TB, Bernstein JA, Maurer M, et al. Similar efficacy with omalizumab in chronic idiopathic/spontaneous urticaria despite different background therapy. *J Allergy Clin Immunol Pract*. 2015;3:743–750.e1.
10. Sussman G, Hébert J, Gulliver W, et al. Omalizumab re-treatment and step-up in patients with chronic spontaneous urticaria: OPTIMA trial. *J Allergy Clin Immunol Pract*. 2020;8:2372–2378.e5.