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Angioedema in the omalizumab chronic idiopathic/spontaneous urticaria pivotal studies

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ABSTRACT

Background: Angioedema, present in some patients with chronic idiopathic/spontaneous urticaria (CIU/CSU), may have a negative effect on patient quality of life.
Objective: To describe patient-reported angioedema and its management in the pivotal omalizumab studies (ASTERIA I, ASTERIA II, GLACIAL).
Methods: Enrolled patients with CIU/CSU remained symptomatic despite treatment with histamine$_1$ (H_1)-antihistamines at licensed doses (ASTERIA I, ASTERIA II) or H_1-antihistamines at up to 4 times the approved dose plus H_2-antihistamines and/or a leukotriene receptor antagonist (GLACIAL). All studies administered omalizumab (75, 150, or 300 mg in ASTERIA I and ASTERIA II; 300 mg in GLACIAL) or placebo subcutaneously every 4 weeks for at least 12 weeks. Urticaria Patient Daily Diary entries were completed by patients and summarized.
Results: At baseline, angioedema prevalence was higher in GLACIAL (53.1%) than in ASTERIA I (47.5%) or ASTERIA II (40.7%). The mean proportion of angioedema-free days during weeks 4 to 12 was greater for patients treated with 300 mg of omalizumab than placebo in ASTERIA I (96.1% vs 88.2%, $P < .001$), ASTERIA II (95.5% vs 89.2%, $P < .001$), and GLACIAL (91.0% vs 88.7%, $P = .006$). Most patient-reported angioedema was managed by low-intensity interventions (doing nothing or taking medication).
Conclusion: Treatment with 300 mg of omalizumab was efficacious in reducing patient-reported angioedema. Low-intensity interventions were generally used to manage angioedema episodes.
Trial Registration: clinicaltrials.gov Identifiers: NCT01287117 (ASTERIA I), NCT01292473 (ASTERIA II), and NCT01264939 (GLACIAL).

Introduction

Chronic idiopathic/spontaneous urticaria (CIU/CSU) is characterized by the spontaneous appearance of hives, angioedema, or both that recur without specific external stimuli for at least 6 weeks.[1,2] Angioedema, which is the acute deeper swelling of the lower dermis or subcutaneous tissue, has been reported to occur in approximately 40% of patients with CIU/CSU.[3–5] CIU/CSU, with and without angioedema, has a negative effect on health-related quality of life.[6]

Since the 1950s, antihistamines have been available to treat urticaria.[2] The nonsedating histamine$_1$ (H_1)-antihistamines were introduced decades later to address issues of sedation. For years, H_1-antihistamines were the only approved treatment for patients with CIU/CSU.[2] Even with H_1-antihistamine use at approved doses, many patients remain symptomatic.[1] Treatment with H_1-antihistamines at up to 4 times the approved dose has been used; however, many patients still remain symptomatic.[1,7,8]

Omalizumab (Genentech Inc, South San Francisco, California, and Novartis Pharmaceuticals Corporation, East Hanover, New

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Jersey) is a humanized anti-IgE monoclonal antibody that has been approved in Europe as add-on therapy for the treatment of CSU in adults and adolescents at least 12 years of age with inadequate response to H_1-antihistamines and in the United States for the treatment of CIU in adults and adolescents at least 12 years of age who remain symptomatic despite H_1-antihistamine treatment.[9,10] The omalizumab phase 3 clinical trials included patients with CIU/CSU who remained symptomatic despite H_1-antihistamine treatment at licensed doses (ASTERIA I, ASTERIA II) or H_1-antihistamine treatment at up to 4 times the approved dose in combination with H_2-antihistamines and/or a leukotriene receptor antagonist (LTRA; GLACIAL).[11–13] In these populations, treatment with omalizumab significantly improved CIU/CSU symptoms. Updated treatment guidelines and practice parameters now include a recommendation for omalizumab as add-on therapy to second-generation H_1-antihistamines for the treatment of CIU/CSU.[2,14]

In all the omalizumab phase 3 studies in CIU/CSU, the presence of angioedema and its management were reported by patients via an electronic daily diary. This article describes patient-reported angioedema and its management from baseline to week 12 in ASTERIA I and II as well as GLACIAL. Data from ASTERIA I and GLACIAL from weeks 12 to 24 also are reported.

Methods

Omalizumab Phase 3 Studies

A summary of key pivotal study details is given in Table 1. ASTERIA I and ASTERIA II were phase 3, global, randomized, multicenter, double-blind, placebo-controlled clinical trials designed to assess the efficacy and safety of omalizumab in patients with CIU/CSU. In ASTERIA I, patients who remained symptomatic despite treatment with H_1-antihistamines at licensed doses were randomized 1:1:1:1 to receive omalizumab (75, 150, or 300 mg) or placebo subcutaneously every 4 weeks for 24 weeks (6 doses) with 16 weeks of additional observational follow-up. In ASTERIA II, patients who remained symptomatic despite treatment with H_1-antihistamines at licensed doses were randomized 1:1:1:1 to receive omalizumab (75, 150, or 300 mg) or placebo subcutaneously every 4 weeks for 12 weeks (3 doses) followed by an additional 16 weeks of observation. The primary end point in both studies was change in the weekly itch severity score from baseline to week 12. Further study details can be found elsewhere.[12,13]

GLACIAL also was a phase 3, global, randomized, multicenter, double-blind, placebo-controlled clinical trial that assessed the safety and efficacy of omalizumab in patients with CIU/CSU. In contrast to ASTERIA I and II, patients were included in GLACIAL after combination therapy failed (H_1-antihistamines at up to 4 times the recommended dose plus H_2-antihistamines and/or LTRAs). Enrolled patients were randomized 3:1 to receive 300 mg of omalizumab or placebo subcutaneously every 4 weeks for 24 weeks (6 doses) with 16 weeks of follow-up. The primary objective of this study was to evaluate the safety of 300 mg of omalizumab vs placebo. The key efficacy end point was change in the weekly itch severity score from baseline to week 12. Further study details can be found elsewhere.[11]

All studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice guidelines and all local regulatory requirements. This was a secondary analysis of clinical trials; detailed institutional review board approval and informed consent were not applicable.

Data Collection

In all 3 studies, patients were given an electronic handheld device (eDiary) at day −14 and completed the components of the Urticaria Patient Daily Diary (UPDD)[15,16] twice per day for the study duration. The UPDD questions included itch severity, number of hives, largest hive size, sleep interference, daily activities interference, diphenhydramine (rescue medication) use, angioedema episodes and management, and health care professional contact for CIU/CSU. The clinical trials collected angioedema status 2 weeks before randomization. Baseline angioedema status was defined as reporting angioedema 7 days before the randomization date and was obtained from patient-reported data in the eDiary (yes/no, rapid swelling [angioedema] of the face, mouth, or elsewhere in the last 24 hours). If they answered this question positively, they were further questioned about what they did in response to angioedema: (1) did nothing; (2) took medication; (3) called the health care professional; (4) went to see the health care professional; or (5) went to the emergency department (ED) at the hospital. Patients were able to select all responses that applied.

Angioedema End Points

The proportion of angioedema-free days from weeks 4 to 12 of therapy was a prespecified secondary end point for all 3 studies. The proportion of angioedema-free days from weeks 4 to 12 was calculated as a ratio. The numerator comprised the number of days for which the patient indicated a no response to a UPDD angioedema question described above. The denominator comprised the total number of patient days with a nonmissing diary entry, starting at the week 4 visit date and ending the day before the week 12 visit date. Patients who withdrew before the week 4 visit or who had missing responses for more than 40% of the daily diary entries between the week 4 and 12 study visits were not included in this analysis. No imputations were performed for missing data. Exploratory analyses in these 3 phase 3 studies included the proportion of patients reporting angioedema by study week and, for those patients reporting angioedema during a particular week, the number of days that angioedema was present in that week and how the angioedema was managed. We present data obtained during the full study period: active treatment (12

Table 1
Key study design features of ASTERIA I, ASTERIA II, and GLACIAL

Feature	ASTERIA I[13]	ASTERIA II[12]	GLACIAL[11]
Background therapy	Approved doses of H_1-antihistamines	Approved doses of H_1-antihistamines	Up to 4 times the approved dose of H_1-antihistamines plus LTRA or H_2-antihistamine or all 3 in combination
Study drugs	Placebo; 75, 150, 300 mg of omalizumab	Placebo; 75, 150, 300 mg of omalizumab	Placebo; 300 mg of omalizumab
No. of doses	6	3	6
Dosing weeks	0, 4, 8, 12, 16, 20	0, 4, 8	0, 4, 8, 12, 16, 20
Efficacy end point	Week 12	Week 12	Week 12
Follow-up period, wk	16	16	16
Total study duration, wk	40	28	40

Abbreviations: H_1, histamine$_1$; LTRA, leukotriene receptor antagonist.