Ann Allergy Asthma Immunol 118 (2017) 500–504

Contents lists available at ScienceDirect

Clinical features of adolescents with chronic idiopathic or spontaneous urticaria

Review of omalizumab clinical trials

Stanley Goldstein, MD [*]; Susan Gabriel, MSc [†]; Farid Kianifard, PhD [†]; Benjamin Ortiz, MD [‡]; David P. Skoner, MD [†]

[*] Allergy and Asthma Care of Long Island, New York, New York
[†] Department of Medicine, Allegheny General Hospital, Pittsburgh, Pennsylvania
[‡] Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

ARTICLE INFO

Article history:
Received for publication November 11, 2016.
Received in revised form February 1, 2017.
Accepted for publication February 6, 2017.

ABSTRACT

Background: Adults and adolescents were included in 3 phase 3 omalizumab trials in chronic idiopathic urticaria (CIU): ASTERIA I, ASTERIA II, and GLACIAL.
Objective: To describe the baseline clinical profile of adolescent patients with CIU enrolled in the omalizumab trials to add to the limited literature available on CIU in this population.
Methods: Data for patient demographics, baseline clinical disease characteristics, medical history, and previous CIU medication information (not efficacy assessments) from phase 3 omalizumab trials were pooled and descriptive statistical analyses performed for adolescent (12 to <18 years old) and adult (≥18 years old) subgroups. Inferential analysis was inappropriate, partly because of small sample size in the adolescent subgroup.
Results: The pooled population of 975 patients with CIU included 39 adolescents (4.0%). Demographics of adolescents and adults with CIU were similar, but compared with adults, fewer adolescents had positive Chronic Urticaria Index test results. Baseline clinical disease characteristics were also similar between the subgroups, with the number of previous CIU medications slightly lower in adolescents compared with adults. Medical history and existing conditions in adolescents tended to be more allergy than cardiovascular related, and fewer experienced angioedema compared with adults.
Conclusion: Pooled data indicate differences in baseline demographic and clinical characteristics between adult and adolescent patient subgroups. This finding helps augment our understanding of the clinical profile of CIU in adolescents, but larger-scale studies in this population are warranted.
Trial Registration: ClinicalTrials.gov Identifiers: NCT01287117 (ASTERIA I), NCT01292473 (ASTERIA II), and NCT01264939 (GLACIAL).

Introduction

Urticaria, characterized by the development of wheals, is considered chronic (chronic urticaria [CU]) if it persists for 6 weeks or longer.[1,2] In cases where no underlying cause can be identified, the term *chronic idiopathic urticaria* (CIU) is used.[2] CIU can be associated with the development of angioedema.[1,2] The term *CIU* is

Reprints: Stanley Goldstein, MD, Allergy and Asthma Care of Long Island, 242 Merrick Road, Ste 401, Rockville Centre, New York, NY 11570; E-mail: drsgoldstein@gmail.com.
Disclosures: Dr Goldstein reported serving on advisory boards for Meda and Novartis; receiving funding for clinical research from Astra Zeneca, Genentech, Merck, Mylan, Novartis, Perrigo, and Teva; and serving on speaker's bureaus for Genentech, GSK, Meda, Merck, Mylan, and Teva. Ms Gabriel reported being an employee of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, at the time of development of this manuscript and remains a stockholder. Drs Kianifard and Ortiz reported being employees and stockholders of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey. Dr Skoner reported receiving grant/research support from Greer, Novartis, Genentech, Merck, GlaxoSmithKline, Sunovion, and Teva; acting as consultant to Merck, Sunovion, Mylan, Teva, Greer, and Meda; and serving on speaker's bureaus for Merck, Genentech, Novartis, Sunovion, Meda, and Greer.
Funding Sources: Development of this study was supported by Novartis Pharmaceuticals Corporation, East Hanover, New Jersey. The ASTERIA I, ASTERIA II, and GLACIAL studies were funded by Genentech Inc, South San Francisco, California, and Novartis Pharma AG, Basel, Switzerland.
Meeting Presentation: Some of the results within this study were previously presented at the American Academy of Allergy, Asthma & Immunology Annual Meeting; February 22, 2015; Houston, Texas.

http://dx.doi.org/10.1016/j.anai.2017.02.003

commonly used interchangeably with *chronic spontaneous urticaria* (CSU) in the literature, with CIU predominantly used in North America and CSU outside North America.[1,2]

CU encompasses CIU and inducible forms of urticaria.[1,2] The estimated lifetime prevalence of CU based on a representative cross-sectional population survey is 1.8%.[3] Of those diagnosed with CU, estimates of the proportion of cases considered to be CIU range from 66% to 93%.[4] In general, the incidence of CIU is lower in children compared with adults; however, most pediatric studies do not differentiate between children (ie, <12 years of age) and adolescents (ie, 12 to <18 years of age). Moreover, there is variation in the age range of patients included in pediatric studies and inconsistency in the reporting of the CU subtype experienced, making it difficult to compare between studies and interpret findings.

Approximately 0.1% to 0.3% of children are affected by CU.[5] Retrospective and prospective studies have investigated the origin of CU in pediatric populations (aged ≤18 years, with variation between studies).[6–15] A systematic review of etiologic factors associated with CU in pediatric patients identified CIU as the most common diagnosis overall (56% of cases); however, this was not consistently observed in all the individual studies included.[16] Across the included studies, the estimated proportion of CU cases defined as idiopathic ranged from 29% to 75%.[7–12,16] Harris et al,[6] in a retrospective study, reported an unknown cause for 79 of 94 pediatric patients with CU (84%), exceeding the upper range of this estimate.[6] Similarly, Kilic et al[17] were unable to identify a cause of CU for 27 of 40 pediatric patients (68%) admitted to a tertiary care center during a 1-year period, with 50% of the study population considered to have CIU based on clinical and laboratory findings. Conversely, 2 historic studies reported rates of unknown or uncertain diagnosis of 25% and 1 study[13–15] reported 13% among pediatric patients with CU. The observed differences among the studies may be in part attributable to differences in study design, including the methods used to confirm diagnosis and the enrolled patient population. On the basis of these studies, no clear conclusions can be drawn with regard to whether there is a predominance for CIU in male or female children.[10,17,18]

Evidence suggests that more than 10% of children with CIU fail to experience satisfactory resolution of symptoms despite treatment with high-dose antihistamines, even with the addition of oral corticosteroids.[19] As for adults, treatment options for children unresponsive to antihistamines include short-term corticosteroid use, immunosuppressants, anti-inflammatory agents (eg, dapsone, montelukast), cyclosporine, or omalizumab, but their use should be based on individual clinical presentation, taking into consideration potential positive and negative outcomes.[1,2] As is evident from the literature summary, the availability of information on CIU in adolescents is limited. Analysis of data from the subgroup of adolescent patients aged 12 to younger than 18 years in 3 phase 3 studies of omalizumab (ASTERIA I, ASTERIA II, and GLACIAL) provides an opportunity to further investigate the clinical manifestation of CIU in this patient population.

The objective of this article is to describe the baseline clinical profile of the adolescent subgroup of patients with CIU enrolled in the randomized, placebo-controlled omalizumab trials to heighten awareness of CIU in adolescents and add to the limited literature. Because of the limited number of adolescent patients, efficacy of omalizumab in the adolescent CIU population is not considered within the scope of this article.

Methods

ASTERIA I (ClinicalTrials.gov Identifier: NCT01287117), ASTERIA II (ClinicalTrials.gov Identifier: NCT01292473), and GLACIAL (ClinicalTrials.gov Identifier: NCT01264939) were randomized, double-blind, controlled phase 3 clinical studies of omalizumab in patients with refractory CIU, the full details of which have been published previously.[20–22]

Briefly, patients (aged 12–75 years and aged 18–75 years in Germany) were eligible for enrollment in these studies provided they met the following inclusion criteria: had been diagnosed with CIU 6 or more months prior; had an urticaria activity score (UAS) during 7 days (UAS7)[23] of 16 or higher and weekly itch severity score (ISS) of 8 or higher for the 7 days before randomization[24,25]; and an in-clinic UAS of 4 or higher at day −14, day −7, and/or the screening visit.[20–22] Patients were required to have experienced hives and angioedema for 8 weeks or more and remained symptomatic despite treatment with approved doses of histamine$_1$ (H_1)–antihistamines in ASTERIA I and ASTERIA II.[20,21] In GLACIAL, patients were required to have experienced symptoms for more than 6 weeks and remained symptomatic despite standard combination therapy (up to 4 times the approved dose of H_1-antihistamines, plus histamine$_2$ [H_2]–antihistamines, leukotriene receptor antagonists, or both H_2-antihistamines and leukotriene receptor antagonists).[22] Exclusion criteria for all studies included a clearly defined underlying cause for the patient's urticaria (eg, physical triggers) and routine doses (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 the screening visit 14 days before randomization (day −14).[20–22] In addition, in ASTERIA I and II, the use of any H_2-antihistamine or leukotriene receptor antagonist within 7 days preceding day −14 and the use of H_1-antihistamines at greater-than-licensed doses within 3 days preceding day −14 was excluded.[20,21]

Baseline assessments included general medical history and previous medications (electronic case report form), clinical characteristics (eg, UAS, largest hive size, sleep interference, and presence of angioedema based on information collected in the Urticaria Patient Daily Diary [UPDD]),[24,25] patient-reported outcomes, and laboratory assessments, including the Chronic Urticaria Index (Viracor-IBT Laboratories, Lee's Summit, Missouri),[20] a second-generation histamine release–urticaria test to evaluate the presence of reactive autoantibodies to the high-affinity IgE receptor and total serum IgE.

Study protocols were reviewed by the institutional review board or ethics committee at each participating center. Before participation, informed written consent was obtained from all patients or their representative if younger than 18 years.[20–22]

In the current post hoc descriptive statistical analysis, baseline data from ASTERIA I, ASTERIA II, and GLACIAL were pooled. Patient demographics, baseline clinical disease characteristics, medical history and baseline conditions, and previous medications for CIU were retrospectively analyzed and summarized for the following subgroups: adolescents (aged 12 to <18 years) and adults (aged ≥18 years). Inferential statistical analysis was deemed inappropriate because of methodologic issues in comparing 2 nonrandomized subgroups and the small sample size in the adolescent subgroup (only 39 patients).

Results

Overall, 975 patients aged 12 to 75 years, of which 39 (4.0%) were adolescents, with CIU who remained symptomatic despite treatment were investigated in the ASTERIA I, ASTERIA II, and GLACIAL trials.

Pooled patient demographics across the 3 omalizumab trials are summarized in Table 1. The mean (SD) age of the adolescent subgroup was 15.1 (1.5) years; adults had a mean (SD) age of 43.4 (13.2) years. In both the adolescent and adult subgroups, most patients were female (adolescents, 69.2%; adults, 73.6%) and white (adolescents, 84.6%; adults, 85.5%), with a mean (SD) body mass index (a measure of weight in kilograms divided by the square of height in