



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).

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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>

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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 histamine₁ (H₁)–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 H₁-antihistamines, plus histamine₂ [H₂]–antihistamines, leukotriene receptor antagonists, or both H₂-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 H₂-antihistamine or leukotriene receptor antagonist within 7 days preceding day –14 and the use of H₁-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 non-randomized 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

Table 1Baseline Patient Demographics (All Patients Who Received at Least 1 Dose Of Study Drug)^a

Demographic	Adolescents (12 to <18 years old) (n = 39)	Adults (≥18 years old) (n = 936)
Age, mean (SD), y	15.1 (1.5)	43.4 (13.2)
Female	27 (69.2)	689 (73.6)
White race	33 (84.6)	800 (85.5)
BMI, mean (SD) (n = 934 adults)	24.4 (4.7)	29.9 (7.3)
Positive Chronic Urticaria Index test result (n = 932 adults)	7 (17.9)	270 (29.0)
Total IgE level, mean (SD), IU/mL (n = 34 adolescents and 906 adults)	148.8 (221.2)	170.4 (311.4)
Median	91.5	79.0
Duration of CIU, mean (SD), y (n = 38 adolescents and 918 adults)	3.2 (3.7)	7.1 (9.2)

Abbreviations: BMI, body mass index; CIU, chronic idiopathic urticaria; CU, chronic urticaria.

^aData are presented as number (percentage) of patients unless otherwise indicated.

meters) of 24.4 (4.7) and 29.9 (7.3), respectively. A Chronic Urticaria Index test result was positive in 17.9% of adolescents and 29.0% of adults. The mean (SD) total IgE level for patients at baseline was elevated: 148.8 (221.2) IU/mL for adolescents and 170.4 (311.4) IU/mL for adults (reference adult range, 13.2–127.0 IU/mL). Adolescents tended not to have experienced CIU for as long as adults (mean [SD], 3.2 [3.7] and 7.1 [9.2] years, respectively).

The mean cumulative UAS7, weekly ISS, and weekly number of hives, the size of the largest hive, interference with sleep and daily activities scores, and the score on most items of the measures of

Table 2Baseline Clinical Disease Characteristics (All Patients Who Received at Least 1 Dose of Study Drug)^a

Characteristic	Adolescents (12 to <18 years old) (n = 39)	Adults (≥18 years old) (n = 936)
In-clinic UAS ^b	5.0 (0.8)	5.3 (0.8)
UAS7 ^b	28.6 (5.7)	31.0 (6.7)
Weekly ISS ^b	13.3 (3.4)	14.1 (3.6)
Weekly number of hives score ^b	15.3 (4.0)	16.9 (4.3)
Weekly size of largest hive score ^b	14.8 (4.2)	15.3 (4.1)
Weekly interference with sleep score ^b	9.0 (4.8)	12.0 (4.9)
Weekly interference with daily activities score ^b	11.6 (3.7)	12.8 (4.5)
Presence of angioedema, n (%)	11 (28.2)	449 (48.0)
Overall DLQI score (n = 930 adults)	12.0 (5.2)	13.3 (6.6)
MOS		
Optimal sleep (n = 927 adults)	0.6 (0.5)	0.4 (0.5)
Short of breath (n = 928 adults)	25.6 (29.7)	19.2 (25.0)
Sleep adequacy (n = 932 adults)	40.8 (23.3)	38.4 (23.9)
Sleep disturbance (n = 932 adults)	49.9 (23.5)	50.2 (24.3)
Sleep Problems Index I (n = 932 adults)	49.7 (19.1)	45.9 (18.4)
Sleep Problems Index II (n = 932 adults)	50.9 (19.4)	48.2 (18.8)
Sleep quantity (n = 929 adults)	7.4 (1.2)	6.3 (1.4)
Snoring (n = 925 adults)	21.0 (29.4)	35.1 (32.6)
Somnolence (n = 932 adults)	54.4 (26.1)	39.8 (21.9)
CU-Q2oL overall score (n = 38 adolescents and 811 adults)	36.1 (17.5)	44.1 (17.5)
EuroQoL-5D index score (n = 930 adults)	0.7 (0.3)	0.7 (0.3)

Abbreviations: CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; EuroQoL-5D, European Quality of Life-5 Dimensions; ISS, itch severity score; MOS, measures of sleep; QoL, quality of life; UAS, urticaria activity score; UAS7, UAS during 7 days.

^aData are presented as mean (SD) unless otherwise stated.^bOn the basis of information collected in the patient daily diary.

sleep scale were similar between adolescents and adults (Table 2). The mean (SD) weekly interference with sleep score was 9.0 (4.8) for adolescents and 12.0 (4.9) for adults. Baseline angioedema, during the 7 days before but not including the first day of treatment, was present in 28.2% of adolescents and 48.0% of adults (Table 2). With regard to quality of life, adolescents and adults reported similar levels of impairment, as measured using the overall Dermatology Life Quality Index, the Chronic Urticaria Quality of Life Questionnaire, and the European Quality of Life-5 Dimensions index score (Table 2). Some caution should be applied when comparing the baseline characteristics because there is no control comparison of adolescents and adults without urticaria.

Considering medical history, adolescents tended to have experienced more allergic rhinitis than adults (61.5% and 43.2%, respectively) and asthma (56.4% and 22.3%, respectively), whereas they were less likely to have experienced angioedema (23.1% and 44.8%, respectively) or conditions typically associated with increased age: hypertension (7.7% and 21.5%, respectively), hypercholesterolemia (2.6% and 15.1%, respectively), or coronary artery disease (0.0% and 1.8%, respectively). A similar percentage of adolescents and adults had experienced diabetes mellitus (5.1% and 5.7%, respectively) (Table 3).

Adolescents received a mean (SD) of 4.2 (2.3) previous CIU medications, and adults received 5.0 (2.8). All patients who received at least 1 dose of study drug received H₁-antihistamines (Table 4). In addition to H₁-antihistamines, previous medications for CIU included H₂-receptor antagonists (adolescents, 48.7%; adults, 48.4%); leukotriene receptor antagonists (adolescents, 35.9%; adults, 34.4%), and systemic corticosteroids (adolescents, 33.3%; adults, 46.3%) (Table 4). The most common other medications were the sedating H₁-antihistamine hydroxyzine hydrochloride (adolescents, 25.6%; adults, 15.5%) and doxepin hydrochloride (adolescents, 12.8%; adults, 30.3%).

Discussion

The treatment paradigm for pediatric populations with CIU mirrors that of adults, yet evidence suggests that approximately

Table 3Medical History and Baseline Conditions (All Patients Who Received at Least 1 Dose of Study Drug)^a

Variable	No. (%) of Patients	
	Adolescents (12 to <18 years old) (n = 39)	Adults (≥18 years old) (n = 936)
Allergic rhinitis		
Ever experienced	24 (61.5)	404 (43.2)
Currently active	23 (59.0)	381 (40.7)
Asthma		
Ever experienced	22 (56.4)	209 (22.3)
Currently active	19 (48.7)	180 (19.2)
Angioedema		
Ever experienced	9 (23.1)	419 (44.8)
Currently active	9 (23.1)	370 (39.5)
Hypertension		
Ever experienced	3 (7.7)	201 (21.5)
Currently active	3 (7.7)	196 (20.9)
Diabetes mellitus		
Ever experienced	2 (5.1)	53 (5.7)
Currently active	2 (5.1)	49 (5.2)
Hypercholesterolemia		
Ever experienced	1 (2.6)	141 (15.1)
Currently active	1 (2.6)	128 (13.7)
Coronary artery disease		
Ever experienced	0 (0.0)	17 (1.8)
Currently active	0 (0.0)	16 (1.7)

^aOnly medical history and baseline conditions occurring in 1% or more of adult patients are included. Data are based on information entered in the general medical history electronic case report form at study start. Results are listed in descending order of frequency in the adolescent subgroup.

Table 4Previous Medications for CIU (All Patients Who Received at Least 1 Dose of Study Drug)^a

Medication	Adolescents (12 to <18 years old) (n = 39)	Adults (≥18 years old) (n = 936)
Any medication use	39 (100.0)	936 (100.0)
No. of previous CIU medications, mean (SD)	4.2 (2.3)	5.0 (2.8)
H ₁ -antihistamines	39 (100.0)	935 (99.9) ^b
H ₂ -receptor antagonists	19 (48.7)	453 (48.4)
LTRAs	14 (35.9)	322 (34.4)
Other medications ^c	14 (35.9)	474 (50.6)
Corticosteroids	13 (33.3)	433 (46.3)
Immunosuppressants	0 (0.0)	87 (9.3)

Abbreviations: CIU, chronic idiopathic urticaria; H₁, histamine₁; H₂, histamine₂; LTRA, leukotriene receptor antagonist.^aResults are presented as number (percentage) unless otherwise stated. Data are based on information entered in the general medical history electronic case report form at study start.^bOne patient decided not to receive the study drug and was therefore not included in the modified intention-to-treat population.^cOther medications included hydroxyzine hydrochloride, doxepin hydrochloride, brompheniramine and pseudoephedrine, cold and sinus remedies, and epinephrine. Medications are listed by descending order of frequency in the adolescent subgroup.

10% of pediatric patients with CIU fail to experience satisfactory resolution of symptoms, despite treatment with high-dose antihistamines, even with the addition of oral corticosteroids.^{1,2,19} However, the current literature on CU tends to be aggregated (pediatric and/or adolescents and/or adults); thus, the availability of information on CU in pediatric and adolescent patients is limited, and despite low incidence, this warrants more attention.

In the current post hoc descriptive statistical analyses of pooled demographics, baseline clinical disease characteristics, medical history, and previous CIU medication data from the ASTERIA I, ASTERIA II, and GLACIAL studies (note that no efficacy data were reported in the current article), the adolescent subgroup represented approximately 4% of the clinical trial population of patients with CIU aged 12 to 75 years. This finding could suggest that CIU is of low incidence or potentially misdiagnosed or underdiagnosed in adolescents; however, epidemiologic studies would be needed to confirm this. Other aspects to consider include that (1) adolescent patients could be more responsive to antihistamines than adults, so they were underrepresented in the phase 3 trials because of the moderate UAS7 inclusion criterion; (2) although adolescent patients were excluded in Germany, where only 10.1% of the total population across studies was enrolled, the effect on adolescent enrollment was likely minimal; and (3) a selection bias in the enrollment of patients into the trial attributable to factors such as disease severity, difficulties obtaining informed consent and liability for children, and socioeconomic characteristics that may make it more likely for patients to participate. A further limitation of the pooled analysis is that the 3 trials enrolled adolescent and adult patients according to specific inclusion and exclusion criteria; thus, the study populations may not be representative of the general population of adolescents and adults with CIU. Regardless, the omalizumab clinical studies still provide a valuable opportunity to focus on the baseline characteristics of the 39 adolescent patients with CIU who were enrolled.

The demographics of adolescents and adults with CIU were similar (mostly female, white, and with elevated IgE levels), as were the clinical disease characteristics. However, compared with adults, fewer adolescents had positive results on the Chronic Urticaria Index test (ie, indicative of an autoantibody-associated component of their disease). Medical history and existing conditions in adolescents tended to be related more to allergy than cardiovascular factors. The

number of previous CIU medications were also slightly lower in adolescents compared with adults and tended to be a higher-level recommendation based on the US Practice Parameter² (ie, antihistamines rather than corticosteroids or immunosuppressants).

Overall, despite approval by the US Food and Drug Administration for patients as young as 12 years with CIU, there is limited published information based on real-world experience on the use of omalizumab in the subgroup of adolescents with CU and in particular CIU. The small number of adolescents who were enrolled across the phase 3 omalizumab studies (only 39 patients) is clearly a limitation; whether the baseline clinical findings reported can be generalized for this patient population is unknown. This, in combination with the small number of published real-world examples, highlights the need for larger-scale studies that focus on the specific subgroup of adolescents with CIU, such that the efficacy of omalizumab in this subgroup can be assessed. However, the indication that there are potential differences in baseline demographic and clinical characteristics between adult and adolescent patient populations is encouraging; any information that improves our understanding of the clinical profile of CIU in adolescents may help to guide clinical practice.

Acknowledgment

Medical writing and editorial assistance in the development of this article were provided by Christina Mackins-Crabtree, PhD, at Fishawack Communications Oxford, Oxford, England, and statistical/programming support was provided by Pharmaceutical Product Development, LLC (PPD), Wilmington, North Carolina. This service was supported by Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, and Genentech Inc, South San Francisco, California.

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