Real-world use of omalizumab in patients with chronic idiopathic/spontaneous urticaria in the United States

Jacqueline Eghrari-Sabet, M.D.,¹ Ellen Sher, M.D.,² Abhishek Kavati, Ph.D.,³ Dominic Pilon, M.A.,⁴ Maryia Zhdanova, M.A.,⁴ Maria-Magdalena Balp, M.D., M.Sc.,⁵ Patrick Lefebvre, M.A.,⁴ Benjamin Ortiz, M.D.,³ and Jonathan A. Bernstein, M.D.^{6,7}

ABSTRACT

Background: Omalizumab was approved for the treatment of chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria (CSU) in the United States in March 2014.

Objective: This study sought to describe real-world omalizumab use, in the United States, in a large cohort of patients with CIU/CSU.

Methods: Patients with CIU/CSU (ages ≥ 12 years) initiated on omalizumab (index date) with ≥ 12 months of pre- and postindex data were identified in the an insurance claims data base (January 1, 2013, to July 31, 2016). Treatment patterns, including the dosing regimen and continuous use of omalizumab (no gaps for ≥ 60 days), were described during the 12-month postindex follow-up period.

Results: A total of 1546 patients (mean $\pm$ standard deviation [SD] ages, 44 ± 14.5 years; 73.1% women) were identified. Most of the patients (84.5%) were initiated on omalizumab 300-mg dose; 90% maintained the initial dose, 7.5% had a dose increase, and 4.6% had a dose decrease. The mean $\pm$ SD omalizumab treatment duration was 9.1 ± 3.8 months, the mean $\pm$ SD number of omalizumab administrations was 8.3 ± 4.8 , and the mean $\pm$ SD administration frequency was 44 ± 29 days. A proportion of the patients continuously treated with omalizumab for 6, 9, and 12 months was 67.3, 54.8, and 47.4%, respectively. Among the patients who discontinued omalizumab for ≥ 3 months (39.8%), 21% restarted the treatment after a mean $\pm$ SD of 4.4 ± 1.3 months. The proportion of patients who used other CIU/CSU-related medications decreased pre- to postindex (94.8 to 81.1%), with the highest decrease observed in oral corticosteroids (75.7 to 49.9%).

Conclusion: In this large real-world study, the majority of the patients with CIU/CSU were initiated on a 300-mg omalizumab dose and treated without titration up or down for 9 months on average. Most of the patients were continuously treated with omalizumab for ≥ 6 months, and one-fourth of the patients who discontinued treatment resumed it. Moreover, compared with baseline levels, the use of other CIU/CSU-related medications was lower after omalizumab initiation, with the most prominent decrease observed in oral corticosteroids.

(Allergy Asthma Proc 39:191–200, 2018; doi: 10.2500/aap.2018.39.4132)

Chronic idiopathic urticaria (CIU) or chronic spontaneous urticaria (CSU) is a dermatologic condition characterized by itchy hives with or without an-

gioedema and symptoms that lasted ≥ 6 weeks without an apparent trigger.¹ The prevalence of CIU/CSU in the United States is 0.5–1%, and it persists for 1–5 years, with a prolonged duration in patients with more severe symptoms.^{2–4} Second-generation H₁-antihistamines are the current standard of care for CIU/CSU^{4,5}; however, >50% of patients do not achieve symptom control even with drugs administered up to four times the licensed doses.^{2,6} Omalizumab, a biologic that targets immunoglobulin E (IgE), was approved in the United States, in March 2014, for the treatment of adults and adolescents (≥ 12 years old) with refractory CIU/CSU. The U.S. stepwise approach to CIU/CSU therapy recommends omalizumab among other step-4 options, including cyclosporine, other immunosuppressants, and anti-inflammatory agents.⁵

From the ¹Family Allergy and Asthma Care, Gaithersburg, Maryland, ²Atlantic Research Center, LLC, Ocean, New Jersey, ³Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, ⁴Analysis Group, Montréal, Quebec, Canada, ⁵Novartis Pharma AG, Basel, Switzerland, ⁶Bernstein Clinical Research Center, Cincinnati, Ohio and ⁷University of Cincinnati College of Medicine, Cincinnati, Ohio. This research was funded by Novartis Pharmaceuticals Corporation. P. Lefebvre, D. Pilon, and M. Zhdanova are employees of Analysis Group, Inc., a consulting company that has received research grants from Novartis Pharmaceuticals Corporation to conduct this study. A. Kavati and B. Ortiz are employees of Novartis Pharmaceuticals Corporation. M.M. Balp is an employee of Novartis Pharma AG. J. Eghrari-Sabet, E. Sher, and J.A. Bernstein received consulting fees from Novartis Pharmaceuticals Corporation.

Presented in part at the 2017 European Academy of Dermatology and Venereology, September 13–17, 2017, Geneva, Switzerland, and at the 2017 Annual Scientific Meeting of the American College of Allergy, Asthma, and Immunology, October 26–30, 2017, Boston, Massachusetts.

Supplemental data available at www.IngentaConnect.com

Address correspondence to Dominic Pilon, M.A., Analysis Group, Inc, 1000 De La Gauchetière West, Suite 1200, Montréal, QC H3B 4W5 Canada

E-mail address: dominic.pilon@analysisgroup.com

Published online March 7, 2018

Copyright © 2018, OceanSide Publications, Inc., U.S.A.

Clinical trials demonstrated safety and efficacy of omalizumab in CIU/CSU⁷⁻⁹; however, the information on practical aspects of omalizumab use, including treatment duration, dosage, and dose change, is still limited in the United States. A number of international studies investigated experiences with omalizumab in a real-world setting, but these studies were small (≤ 110 patients), and some studies included off-label use of omalizumab.¹⁰⁻¹⁴ A few early U.S. real-world studies of omalizumab in CIU/CSU had a sample size of <300 patients.^{15,16} To the best of our knowledge, this study was among the first to describe characteristics and treatment patterns in a large sample of patients with CIU/CSU initiated on omalizumab in a real-life setting in the United States.

METHODS

Data Source

The Truven Health MarketScan Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits data bases (January 1, 2013, to July 31, 2016) were used. Available data included patient demographics, medical, and prescription drug claims. The data bases cover all U.S. Census regions with a concentration in the South and North Central (Midwest) regions, and allow creation of a nationally representative data sample of Americans with employer-provided health insurance. The data bases are fully compliant with the Health Insurance Portability and Accountability Act; therefore, no ethics review was necessary.

Study Design

In this retrospective descriptive study, the index date was defined as the date of omalizumab initiation. Patient demographics and clinical characteristics as well as the use of preomalizumab CIU/CSU-related medications were reported during the baseline period, defined as the 12 months before the index date. Treatment patterns were analyzed during the follow-up period, which spanned from the index date until the end of data availability for a minimum of 12 months. Sensitivity analyses were conducted in patients with ≥ 18 and 24 months of follow-up.

To be included in the study, the patients were required to have CIU/CSU identified based on the validated algorithm¹⁷: two or more independent claims with a diagnosis for idiopathic (*the International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 708.1x; *the International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM] code L50.1xx), other (ICD-9-CM code 708.8x; ICD-10-CM code L50.8xx), or unspecified urticaria (ICD-9-CM code 708.9x; ICD-10-CM code L50.9xx) ≥ 6 weeks apart or one or more claims with a diagnosis for idio-

pathic, other, or unspecified urticaria; and one or more claims with a diagnosis for angioedema (ICD-9-CM code 995.1x; ICD-10-CM code T78.3) ≥ 6 weeks apart. In addition, the patients were required to have one or more pharmacy or medical claims of omalizumab, with the first claim being after March 21, 2014. The patients without 12 months of continuous health plan eligibility before and after the index date and those <12 years old at the index date were excluded from the study.

Outcome Measures

The baseline use of CIU/CSU-related medications (*i.e.*, oral corticosteroids [OCS], H₁- and H₂-antihistamines, leukotriene receptor antagonists [LTRA], anti-inflammatory and immunosuppressive agents, and antidepressants) was defined as one or more prescription fills of such medication. The number of prescription fills as well as the highest step of the CIU/CSU step-

Figure 1. Sample selection. Data from Truven Health MarketScan Commercial and Medicare Supplemental Databases (January 1, 2013, to July 31, 2016). CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; ICD-9-CM = the International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM = the International Classification of Diseases, Tenth Revision, Clinical Modification. Notes: (1) Idiopathic urticaria: ICD-9-CM code 708.1x and ICD-10-CM code L50.1xx; other urticaria: ICD-9-CM code 708.8x and ICD-10-CM code L50.8xx; unspecified urticaria: ICD-9-CM code 708.9x and ICD-10-CM code L50.9xx; (2) the claims algorithm for identifying patients with CIU/CSU was validated by Ref. 17; and (3) angioedema: ICD-9-CM code 995.1x and ICD-10-CM code T78.3.

care approach achieved during the baseline period were also reported.⁵ Treatment patterns described during the follow-up period included an omalizumab dosing regimen, continuous use of omalizumab at various time points, concomitant use of omalizumab with other CIU/CSU-related medications at the index date, treatment changes associated with omalizumab, and the

use of other CIU/CSU-related medications during the follow-up period.

Omalizumab Dosing Regimen

Omalizumab, available in vials of 150 mg, is indicated in patients with CIU/CSU at one or two vials

Table 1 Patient baseline characteristics (N = 1546)

Characteristics	
Observation period, mean $\pm$ SD (median; Q1–Q3; IQR), days	612 $\pm$ 151 (617; 475–751; 276)
Age, mean $\pm$ SD (median; Q1–Q3; IQR), y*	44.4 $\pm$ 14.5 (45; 35–55; 20)
Women no. (%)	1130 (73.1)
Region of residence, no. (%)*	
South	687 (44.4)
North Central	308 (19.9)
West	266 (17.2)
North East	281 (18.2)
Unknown	4 (0.3)
Type of commercial health care plan, no. (%)*	
PPO	943 (61.0)
Comprehensive	61 (3.9)
CDHP and HDHP	271 (17.5)
HMO and POS with capitation	138 (8.9)
POS and EPO	112 (7.2)
Unknown	21 (1.4)
Medicare coverage, no. (%)*	96 (6.2)
Year of index date, no. (%)	
2014	982 (63.5)
2015	564 (36.5)
Quan-Charlson Comorbidity Index, mean $\pm$ SD (median; Q1–Q3; IQR)#	0.79 $\pm$ 1.09 (0; 0–1; 1)
Angioedema#§	506 (32.7)
Top three CIU/CSU-related comorbidities, no. (%)#§	
Allergic rhinitis	779 (50.4)
Asthma	491 (31.8)
Food and other allergies	327 (21.2)
Top three mental comorbidities, no. (%)#¶	
Anxiety disorders	203 (13.1)
Depressive disorders	198 (12.8)
Sleep-wake disorders	181 (11.7)
Top three cardio- and cerebrovascular comorbidities, no. (%)#§	
Coronary artery disease	48 (3.1)
Sinus tachycardia	39 (2.5)
Stroke and transient ischemic attack	30 (1.9)

SD = standard deviation; Q1 = first quartile; Q3 = third quartile; IQR = interquartile range; PPO = preferred provider organization; CDHP = consumer directed health plan; HDHP = high deductible health plan; HMO = health maintenance organization; POS = point of service; EPO = exclusive provider organization; CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria.

*Measured at the index date.

#Measured during the 12-mo baseline period.

§Diagnostic codes to identify comorbidities are provided in Supplemental Appendix 1.

¶From American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013 May 22.

every 4 weeks. The dosing regimen was assessed in patients with pharmacy claims of omalizumab by using information on the days and the quantity supplied. The initial (index) dose, number and frequency of omalizumab administrations, and dose changes were described.

Continuous Use of Omalizumab

The proportion of the patients who used omalizumab continuously for 6, 9, and 12 months was re-

ported. Continuous omalizumab use was defined as an absence of a gap (*i.e.*, 30, 60, and 90 days) between consecutive days of omalizumab supply or between the last day of omalizumab supply and the end of the follow-up period.

Concomitant Use with Other CIU/CSU-Related Medications at the Index Date

Concomitant use of omalizumab with other CIU/CSU-related medications (*i.e.*, OCS, H₁- and H₂-antihis-

Table 2 Baseline use of CIU/CSU-related medications (N = 1546)

Medications	
Oral corticosteroids, no. (%)	1171 (75.7)
No. fills, mean $\pm$ SD (median; Q1–Q3; IQR)	2.7 $\pm$ 2.8 (2; 1–4; 3)
Leukotriene receptor antagonists, no. (%)	812 (52.5)
No. fills, mean $\pm$ SD (median; Q1–Q3; IQR)	1.9 $\pm$ 2.8 (1; 0–3; 3)
Antidepressants, no. (%) [*]	692 (44.8)
No. fills, mean $\pm$ SD (median; Q1–Q3; IQR)	2.8 $\pm$ 4.7 (0; 0–4; 4)
Prescription H ₁ -antihistamines, first generation, no. (%) [#]	726 (47.0)
No. fills, mean $\pm$ SD (median; Q1–Q3; IQR)	1.5 $\pm$ 2.7 (0; 0–2; 2)
Prescription H ₂ -antihistamines, no. (%) [#]	501 (32.4)
No. fills, mean $\pm$ SD (median; Q1–Q3; IQR)	1.1 $\pm$ 2.2 (0; 0–1; 1)
Prescription H ₁ -antihistamines, second generation, no. (%) [#]	367 (23.7)
No. fills, mean $\pm$ SD (median; Q1–Q3; IQR)	0.9 $\pm$ 2.2 (0; 0–0; 0)
Anti-inflammatory agents, no. (%) [§]	197 (12.7)
No. fills, mean $\pm$ SD (median; Q1–Q3; IQR)	0.5 $\pm$ 1.9 (0; 0–0; 0)
Immunosuppressive agents, no. (%) [¶]	154 (10.0)
No. fills, mean $\pm$ SD (median; Q1–Q3; IQR)	0.4 $\pm$ 1.7 (0; 0–0; 0)
Patterns of treatment based on the step-care approach, no. (%) [#]	
Step 1 ^{**}	37 (2.4)
Step 2 ^{##}	86 (5.6)
Step 3 ^{§§}	614 (39.7)
Step 4 (excluding omalizumab) ^{¶¶}	309 (20.0)
Unclassified	500 (32.3)

CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; SD = standard deviation; Q1 = quartile 1; Q3 = quartile 3; IQR = interquartile range.

^{*}Included doxepin.

[#]Use of antihistamines might be underreported due to over-the-counter medications not being captured in pharmacy claims data.

[§]Included hydroxychloroquine, dapson, colchicine, and sulfasalazine.

[¶]Included cyclosporine, mycophenolate, and methotrexate.

^{||}The highest step during the baseline period was reported (from Ref. 5).

^{**}Defined as the use (≥ 7 days) of second-generation antihistamine alone.

^{##}Defined as the use (≥ 7 days) of one or more of the following: second-generation antihistamine alone in a dose larger than that approved by the U.S. Food and Drug Administration, ≥ 2 second-generation H₁-antihistamines, second-generation H₁-antihistamine with H₂-antihistamine, leukotriene receptor antagonists, or first-generation H₁-antihistamine. Combination patterns were identified based on the overlapping episodes of continuous use. Use was considered continuous if there was no gap of ≥ 30 days between days of supply.

^{§§}Defined as the use (≥ 7 days) of hydroxyzine or doxepin.

^{¶¶}Defined as the use (≥ 7 days) of anti-inflammatory or immunosuppressive agents.

^{||}Patients who did not use prescription second-generation H₁-antihistamines, hydroxyzine, doxepin, anti-inflammatory or immunosuppressive agents remained unclassified.

Percentage of patients with initial dose of omalizumab and dose change

Figure 2. The initial dose of omalizumab and dose change by year of omalizumab initiation. Notes: (1) The initial dose of omalizumab and subsequent dose change were assessed among patients with one or more pharmacy claims; (2) the dose change was defined based on the change in the number of 150-mg vials supplied per 4 weeks. An increase (decrease) compared with the previous prescription represents a dose increase (decrease).

tamines, LTRAs, anti-inflammatory and immunosuppressive agents, and antidepressants) at the index date was defined as a continuous use of a medication (*i.e.*, no gap of ≥ 30 days between consecutive days of the supply) for ≥ 30 days after omalizumab initiation.

Treatment Changes Associated with Omalizumab

Discontinuation of omalizumab was defined as a gap of ≥ 90 days between consecutive days of omalizumab supply or between the last day of omalizumab supply and the end of the follow-up period. A switch from omalizumab was defined as a prescription fill for another CIU/CSU-related medication during the 90-day period after omalizumab discontinuation; the new treatment had to be either discontinued or never used before the switch date. Restart of omalizumab was defined as a gap of ≥ 90 days between consecutive days of omalizumab supply. Add-on to omalizumab was defined as an overlap in continuous use of omalizumab and another CIU/CSU-related medication not used concomitantly at the index date, with one or more refills of omalizumab during the overlap.

Use of Other CIU/CSU-Related Medications During the Follow-up Period

The use of other CIU/CSU-related medications during the follow-up period was defined as one or more prescription fills for such medication. It was described over the entire follow-up period as well as in 3-month intervals postindex to capture potential changes in the use of medications after the omalizumab initiation.

Statistical Analysis

Patient characteristics and treatment patterns were described by using mean $\pm$ SD, median, first and third quartiles, and interquartile range for continuous variables and frequencies and proportions for categorical variables. All statistical analyses were conducted by using SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Characteristics

A total of 91,996 patients with CIU/CSU were identified, among whom 4582 were initiated on omalizumab after March 21, 2014, and 1546 met the remaining selection criteria (Fig. 1). The sample covered all U.S. Census regions, with 44.4% of the patients from the South, 19.9% from the North Central, 18.2% from the North East, and 17.2% from the West region (Table 1). The mean $\pm$ SD duration of the follow-up period was 612 ± 151 days; 946 patients (61.2%) had ≥ 18 months of follow-up, and 447 (28.9%) had ≥ 24 months of follow-up. The majority of the patients with ≥ 18 and 24 months of follow-up were initiated on omalizumab early in 2014. The patients had a mean $\pm$ SD age of 44 ± 14.5 years and were predominately women (73.1%). During the baseline period, 32.7% of the patients had one or more diagnoses of angioedema, and the top three CIU/CSU-related conditions included allergic rhinitis (50.4%), asthma (31.8%), and food and other allergies (21.2%) (diagnostic codes to identify comorbidities are provided in Supplemental Appendix 1). The top

three mental comorbidities included anxiety, depressive, and sleep-wake disorders with a prevalence of 13.1, 12.8, and 11.7%, respectively. The majority of patients (80.5%) had one or more visits to an allergist or immunologist, and 38.7% had one or more visits to a dermatologist.

Baseline Use of Medications

During the baseline period, the majority of patients (75.7%) used an OCS, with the mean $\pm$ SD number of fills being 2.7 ± 2.8 (Table 2). Slightly more than half of the patients (52.5%) used an LTRA, predominantly montelukast (51.5%), with the mean $\pm$ SD number of fills being 1.9 ± 2.8 . Only prescribed H₁-antihistamines were captured in the data, with the use as following: 47.0% used first-generation H₁-antihistamines (mean $\pm$ SD, 1.5 ± 2.7 fills), 32.4% used H₂-antihistamines (mean $\pm$ SD, 1.1 ± 2.2 fills), and 23.7% used second-generation H₁-antihistamines (mean $\pm$ SD, 0.9 ± 2.2 fills). The baseline use of anti-inflammatory and immunosuppressive agents that indicate refractory CIU/CSU was relatively low, at 12.7 and 10.0%, respectively. Close to half of the patients (44.8%) filled one or more prescriptions (mean $\pm$ SD, 2.8 ± 4.7) for an antidepressant, including doxepin. Also, when classifying patients according to the highest step in the U.S. step-care approach to CIU/CSU,⁵ most patients (39.7%) received treatment according to step 3 (*i.e.*, hydroxyzine or doxepin) protocol, which precedes initiation of treatment with omalizumab.

Omalizumab Dosing Regimen

Most patients (84.5%) were initiated on a 300-mg dose of omalizumab. The index dose of 300 mg was slightly less common in patients initiated on omalizumab in 2014 (80.0%) compared with 2015 (92.3%) (Fig. 2) and in patients with longer follow-up. Most patients (90.0%) were maintained on their index dose, 7.5% had a dose increase, and 4.6% had a dose decrease. Among the patients with a dose increase, 39.5% increased to 300 mg and the rest increased to higher doses. Dose increases were more frequent in patients initiated on omalizumab in the first year of its approval (8.0% in 2014 versus 6.6% in 2015). The duration of treatment with omalizumab (mean $\pm$ SD, 273 ± 113 days), number of omalizumab administrations (mean $\pm$ SD, 8.3 ± 4.8) and frequency of administrations (mean $\pm$ SD, 44 ± 29 days) were similar among the patients initiated on 150- and 300-mg doses of omalizumab (Table 3). The patients with ≥ 18 and 24 months of follow-up had a longer duration of treatment with omalizumab (mean $\pm$ SD, 384 ± 179 and 518 ± 242 days, respectively).

Continuous Use of Omalizumab

The majority of the patients (67.3%) were continuously treated with omalizumab for ≥ 6 months without

Table 3 Omalizumab treatment duration, and number and frequency of administrations

	For All Patients (N = 1546)	Initial Dose of 150 mg (n = 78)*	Initial Dose of 300 mg (n = 933)*
Duration of treatment with omalizumab, mean $\pm$ SD (median; Q1–Q3; IQR), days#	273.0 $\pm$ 113.2 (347; 185–363; 178)	285.8 $\pm$ 114.7 (363; 219–363; 144)	273.7 $\pm$ 113.6 (349; 185–363; 178)
No. omalizumab administrations, mean $\pm$ SD (median; Q1–Q3; IQR)	8.3 $\pm$ 4.8 (8; 4–12; 9)	8.1 $\pm$ 4.8 (9; 3–12; 9)	8.0 $\pm$ 4.8 (8; 4–12; 8)
Frequency of administrations, mean $\pm$ SD (median; Q1–Q3; IQR), days	43.9 $\pm$ 29.2 (32; 28–47; 19)	47.0 $\pm$ 31.3 (34; 29–50; 21)	47.0 $\pm$ 31.0 (33; 28–55; 27)

SD = standard deviation; Q1 = first quartile; Q3 = third quartile; IQR = interquartile range.
 *Initial dose of omalizumab was known in patients with one or more pharmacy claims.
 #Included restarts; discontinuation was defined as a gap of ≥ 90 days between consecutive days of omalizumab supply or between the last day of omalizumab supply and the end of the follow-up period.

Figure 3. Continuous use of omalizumab. Note: continuous omalizumab use was defined as an absence of a gap between consecutive days of omalizumab supply or between the last day of omalizumab supply and the end of the follow-up period. Gaps of ≥ 30 , 60, or 90 days were considered.

a gap in treatment of ≥ 60 days. Over time, continuous use of omalizumab displayed a decreasing trend, with fewer than half of the patients (47.4%) continuously treated up to 12 months. Similar trends were observed when using different gap length (*i.e.*, 30 and 90 days) (Fig. 3) and in the patients with ≥ 18 and 24 months of follow-up.

Concomitant Use with Other CIU/CSU-Related Medications at the Index Date and Treatment Changes Associated with Omalizumab

At the index date, 56.5% of patients received one or more other medication with omalizumab (Table 4). The most common combination was with an LTRA (27.8%), followed by an antidepressant (25.9%). The percentages of the patients who used prescription H_1 - and H_2 -antihistamines concomitantly with omalizumab were 21.0 and 14.2%, respectively. Over the follow-up period, 39.8% of the patients discontinued omalizumab for ≥ 3 months with the mean $\pm$ SD time to discontinuation being 131 ± 76 days. Among those who discontinued, 54% switched to another CIU/CSU-related medication (most commonly, to a prescription H_1 -antihistamine), and 21.0% subsequently restarted treatment with omalizumab. An add-on to omalizumab was observed in 34.2% of the patients, with an OCS being the most common medication added (37.7%), followed by a prescription H_1 -antihistamine (25.2%). Among the patients with ≥ 18 and 24 months of follow-

up, higher proportions discontinued omalizumab (50.1 and 53.2%, respectively) and subsequently resumed it (29.1 and 39.5%, respectively).

Use of Other CIU/CSU-Related Medications During the Follow-up Period

Initiation of omalizumab was associated with a decreased use of other CIU/CSU-related medications: 94.8% of the patients had one or more fills of such medication during the baseline period versus 84.6% during the follow-up period (Fig. 4). This decrease occurred across all medications, with the most prominent observed in OCS (75.7% during the baseline versus 49.9% during the follow-up). Furthermore, the use of medications was consistently decreasing during the follow-up period, from 72.8% over the first 3 months to 58.5% over the last 3 months. This trend was observed in all medications with the exception of antidepressants, the use of which remained constant but at a lower level compared with the baseline period.

DISCUSSION

Our study described characteristics and treatment patterns of a large sample of U.S. patients with CIU/CSU initiated on omalizumab in a clinical setting. Patients from all U.S. Census regions were included in the study, and the results were generalizable to the commercially insured U.S. population. Patient demographic char-

Table 4 Concomitant use with other CIU/CSU medications at index date and treatment changes associated with omalizumab (N = 1546)

Treatment patterns	
Medications used concomitantly with omalizumab at the index date, no. (%) [*]	873 (56.5)
Leukotriene receptor antagonists	430 (27.8)
Antidepressants	401 (25.9)
H ₁ -antihistamines	324 (21.0)
H ₂ -antihistamines	219 (14.2)
Oral corticosteroids	162 (10.5)
Anti-inflammatory agents [#]	77 (5.0)
Immunosuppressive agents [§]	38 (2.5)
Discontinuation of omalizumab, no. (%) [¶]	615 (39.8)
Time to first discontinuation, mean ± SD (median; Q1–Q3; IQR), days	131.4 ± 75.9 (127; 68–189; 121)
Switch from omalizumab, no. (%)	335 (54.5)
H ₁ -antihistamines	96 (28.7)
Oral corticosteroids	88 (26.3)
Leukotriene receptor antagonists	62 (18.5)
H ₂ -antihistamines	41 (12.2)
Anti-inflammatory agents [#]	29 (8.7)
Immunosuppressive agents [§]	19 (5.7)
Restart of omalizumab, no. (%) ^{**}	129 (21.0)
Time from discontinuation to restart, mean ± SD (median; Q1–Q3; IQR), days	133.2 ± 39.7 (122; 102–153; 51)
Add-on to omalizumab, no. (%) ^{##}	528 (34.2)
Oral corticosteroids	199 (37.7)
H ₁ -antihistamines	133 (25.2)
Leukotriene receptor antagonists	76 (14.4)
H ₂ -antihistamines	71 (13.4)
Anti-inflammatory agents [#]	32 (6.1)
Immunosuppressive agents [§]	17 (3.2)

CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; SD = standard deviation; Q1 = quartile 1; Q3 = quartile 3; IQR = interquartile range.

^{*}Concomitant use was defined as a continuous use of a CIU/CSU medication (no gap of ≥30 days between consecutive days of supply) for ≥30 days after omalizumab initiation.

[#]Anti-inflammatory agents included hydroxychloroquine, dapson, colchicine, and sulfasalazine.

[§]Immunosuppressive agents included cyclosporine, mycophenolate, and methotrexate.

[¶]Discontinuation was defined as a gap of ≥90 days between consecutive days of omalizumab supply or between the last day of omalizumab supply and the end of the follow-up period.

^{||}Switch was defined as a prescription fill for another CIU/CSU medication during the 90-day period after omalizumab discontinuation; the new treatment had to be either discontinued or never used before the switch date.

^{**}Restart was defined as a gap of ≥90 days between consecutive days of omalizumab supply.

^{##}Add-on was defined as an overlap in continuous use of omalizumab and another CIU/CSU treatment not used concomitantly at the index date, with one or more refills of omalizumab during the overlap.

acteristics were comparable with those reported in clinical trials.^{7–9} In terms of severity, the prevalence of angioedema, which can be considered an unfavorable prognostic factor, was lower in our study (32.7%) compared with a range of 38–54% in trials.^{7–9} Preomalizumab use of immunosuppressive agents was similar to that in the GLACIAL trial.⁷ The patients in our study

had a slightly lower preomalizumab use of LTRAs (52.5% compared with 57.5% in the GLACIAL trial); however, the use of OCS was higher, at 75.7% compared with 57.9% in the GLACIAL trial.

In our study, the majority of the patients were initiated on a 300-mg dose of omalizumab. In early real-world studies, patients were reported to predominantly start

Figure 4. Utilization (from Ref. 1) of other CIU/CSU medications after omalizumab initiation. CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria. Note: (1) Utilization is defined as one or more prescription fills for a corresponding medication; (2) anti-inflammatory agents included hydroxychloroquine, dapsone, colchicine, and sulfasalazine; and (3) immunosuppressive agents included cyclosporine, mycophenolate, and methotrexate.

omalizumab with a 150-mg dose.^{11,13,14} In our study, more patients were initiated on a 300-mg dose in the second versus the first year after approval of omalizumab, a change in prescribing practice that could be related to publications that show improved efficacy of omalizumab in CIU/CSU when administered as a 300-mg dose.¹⁸ Among the patients with a dose increase, 60.5% increased the dose to >300 mg. This finding should be interpreted with caution because the number of patients to increase the dose to >300 mg was small ($n = 46$). Moreover, the majority initiated omalizumab shortly after its approval (in 2014, $n = 29$), and such dose increases could be due to limited clinical experience with the drug. Of note, one clinical trial examined the use of the 600 mg of omalizumab but did not find it to be more effective than the 300-mg dose.¹⁹

At 6 months, which corresponds to the duration of treatment with omalizumab in the ASTERIA I⁹ and GLACIAL⁷ trials, and exceeds the treatment length in the ASTERIA II⁸ trial, >50% of the patients remained treated with omalizumab, which indicates that omali-

zumab might be administered for >6 months in approximately one-half of the patients. Among the patients who discontinued omalizumab for ≥ 3 months, 21% restarted the treatment. Clinical^{7,8,20} and real-world studies^{10,11,13} reported a possibility of symptom reoccurrence once omalizumab is discontinued, which could be one of the reasons to restart omalizumab. Reasons for omalizumab discontinuation and restarting were not available in the claims data; however, another study reported the lack of time for treatment, insurance disenrollment, and symptom resolution among the top reasons for omalizumab discontinuation that might lead to a subsequent restart of omalizumab.¹⁵

The use of other CIU/CSU-related medications in our study decreased after omalizumab initiation compared with baseline levels. A numerical decrease of 25 percentage points in the proportion of patients who used OCS exceeded that reported in a recent real-world study.¹⁵ This was an important finding given an increased risk of adverse effects reported in patients

with CIU/CSU treated with OCS.²¹ Evidence of decreased utilization of other CIU/CSU-related medications after omalizumab initiation was also reported in another real-world study.¹²

Study Limitations

This study was subject to a number of limitations. Only prescription H₁-antihistamines are captured in pharmacy claims, and, because H₁-antihistamines could be obtained over the counter, the current study likely underreported their use. The dose of omalizumab injections administered in a medical setting cannot be identified in claims data, hence, only patients with one or more pharmacy claims were considered for the analysis of the omalizumab dosing regimen. A pharmacy claim corresponds to an order of the drug and provides an approximation on the actual dose and frequency of the drug administration; moreover, a pharmacy claim does not guarantee that the medication was taken, which potentially led to overestimation of medication use. Of note, omalizumab use was described based on both pharmacy claims and medical claims for injections, the latter served as a guarantee that the medication was administered. Also, administrative claims data might have inherent limitations, such as potential miscoding or may contain inaccurate or missing data on prescriptions, procedures, and diagnoses.

CONCLUSION

In this large real-world study of patients with CIU/CSU who were treated with omalizumab, the majority were initiated on a 300-mg dose and received the medication for an average of 9 months without dose titration up or down. Most of the patients were continuously treated with omalizumab for ≥ 6 months. Among patients who discontinued omalizumab for ≥ 3 months, one-fourth resumed it. The discontinuation and restart rates were higher in the patients with longer follow-up. The use of CIU/CSU-related medications decreased after omalizumab initiation compared with baseline levels and displayed a declining trend during the follow-up period.

REFERENCES

- Greaves MW, Tan KT. Chronic urticaria: recent advances. *Clin Rev Allergy Immunol*. 2007; 33:134–143.
- Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. *Allergy*. 2011; 66:317–330.
- Toubi E, Kessel A, Avshovich N, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy*. 2004; 59:869–873.
- Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: The 2013 revision and update. *Allergy*. 2014; 69:868–887.
- Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014; 133:1270–1277.
- Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010; 125:676–682.
- Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013; 132:101–109.
- Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013; 368:924–935.
- 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; 135:67–75.
- Bongiorno MR, Crimi N, Corrao S, et al. Omalizumab for the treatment of chronic spontaneous urticaria in clinical practice. *Ann Allergy Asthma Immunol*. 2016; 117:703–707.
- Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: A retrospective clinical analysis. *J Dermatol Sci*. 2014; 73:57–62.
- Labrador-Horrillo M, Valero A, Velasco M, et al. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. *Expert Opin Biol Ther*. 2013; 13:1225–1228.
- Sussman G, Hébert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol*. 2014; 112:170–174.
- Rottem M, Segal R, Kivity S, et al. Omalizumab therapy for chronic spontaneous urticaria: The Israeli experience. *Isr Med Assoc J*. 2014; 16:487–490.
- Wang L, Ke X, Kavati A, et al. Real-world treatment patterns and outcomes of omalizumab use in patients with chronic idiopathic urticaria. *Curr Med Res Opin*. 2018; 34:35–39.
- Ke X, Kavati A, Wertz D, et al. Real-world characteristics and treatment patterns in patients with urticaria initiating omalizumab in the United States. *J Manag Care Spec Pharm*. 2017:1–11.
- Cherepanov D, Raimundo K, Chang E, et al. Validation of an ICD-9-based claims algorithm for identifying patients with chronic idiopathic/spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2015; 114:393–398.
- Kaplan A, Ferrer M, Bernstein JA, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. *J Allergy Clin Immunol*. 2016; 137:474–481.
- Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011; 128:567–573.e1.
- Gimenez-Arnau AM, Toubi E, Marsland AM, Maurer M. Clinical management of urticaria using omalizumab: the first licensed biological therapy available for chronic spontaneous urticaria. *J Eur Acad Dermatol Venereol*. 2016; 30(suppl 5):25–32.
- Ledford D, Broder MS, Antonova E, Omachi TA, Chang E, Luskin A. Corticosteroid-related toxicity in patients with chronic idiopathic urticaria-chronic spontaneous urticaria. *Allergy Asthma Proc*. 2016; 37:458–465. □