

# Long-term omalizumab outcomes in chronic idiopathic urticaria: a real-world study

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## ABSTRACT

**Background:** Although clinical trials documented omalizumab's efficacy in U.S. patients with chronic idiopathic urticaria (CIU), the real-world evidence on its long-term effectiveness is lacking.

**Objective:** To assess omalizumab use and the long-term response in a large sample of U.S. real-world patients.

**Methods:** Patients with CIU and  $\geq 12$  years old who were initiated on omalizumab (index date) and with  $\geq 6$  months of postindex data were identified in an electronic medical record system (2007–2018). Omalizumab use was described. Provider assessments of disease control and course, and patient-reported symptoms were compared at 6-month intervals postindex versus baseline in the patients with values available at both time points.

**Results:** A total of 1096 patients (mean age, 44.1 years; 74.7% women) were followed up for a mean of 19 months postindex. Patients, predominantly initiated on a 300-mg dose, received a mean of 15 omalizumab administrations and were treated continuously for a mean of 14.2 months. At 6 months postindex versus baseline, the patients ( $n = 708$ ) were more likely to be well controlled (odds ratio [OR] 31.68 [95% confidence interval {CI}, 17.20–58.36]) with an improved disease course (OR 15.73 [95% CI, 11.33–21.85]). Moreover, the patients ( $n = 373$ ) were less likely to report itching (OR 0.39 [95% CI, 0.21–0.76]), rash (OR 0.59 [95% CI, 0.45–0.78]), and swelling (OR 0.46 [95% CI, 0.36–0.59]). Benefits associated with omalizumab treatment were sustained through month 24 and beyond.

**Conclusion:** This real-world study showed that the patients who received a mean of 15 omalizumab administrations over a mean of 14.2 months experienced, starting at 6 and through 24 months after omalizumab initiation and beyond, improved CIU control, course, and symptoms.

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Chronic idiopathic urticaria (CIU) is a dermatologic condition characterized by wheals, angioedema, or both, with no apparent inducible factor, which last 6 weeks<sup>1</sup> to, typically, 1–5 years.<sup>2</sup> CIU affects 0.5–1% of the population in the United States<sup>2</sup> and is associated with a lower quality of life, depression and anxiety, and a high disease burden.<sup>1,3–6</sup> Omalizumab, a recom-

binant humanized monoclonal antibody that targets serum immunoglobulin E, is a recent therapeutic advance for CIU. In March 2014, the U.S. Food and Drug Administration approved omalizumab for the treatment of CIU in adults and adolescents  $\geq 12$  years of age with refractory CIU unresponsive to H<sub>1</sub>-antihistamines. Subsequently, international urticaria treatment guidelines recommended omalizumab as an add-on to upodused second-generation antihistamines in the third-line treatment of CIU.<sup>7</sup>

Although efficacy and safety of omalizumab for CIU treatment is well documented in clinical trials,<sup>8–14</sup> real-world evidence on its effectiveness remains limited. Previous U.S. real-world studies had a small sample size and/or included patients who received omalizumab off-label.<sup>15–18</sup> By using electronic medical records (EMR), this study aimed to provide a comprehensive review of outcomes associated with omalizumab treatment in U.S. patients with CIU observed in a clinical practice.

## METHODS

### Data Source

Data were retrieved from the EMR system (January 1, 2007, to June 30, 2018) of Allergy Partners (AP)

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(Allergy Partners P.A., Asheville, North Carolina), the largest single-specialty practice in allergy, asthma and immunology in the United States. The AP network consists of > 120 providers and spans 21 U.S. states (with a concentration in the South), and encompasses > 110 locations of service. The study did not use any patient-identifiable information and was exempt from an independent review board review by the New England Independent Review Board.

## Study Design

In this retrospective observational study, the index date was defined as the first administration of omalizumab. The baseline period spanned  $\leq 12$  months before the index date and included the index date. No minimum duration of the baseline period was required, but patients had one or more medical visits to an AP clinic on or before the index date, which ensured availability of some baseline information. Patient characteristics were captured during the baseline period, with the exception of the pre-omalizumab CIU treatment history (obtained from the structured EMR and from the chart abstraction), which was reported any time before the index date. The follow-up period spanned  $\geq 6$  months from the index date until the end of data availability (June 30, 2018) or the last visit to an AP clinic.

The study was conducted in patients with CIU who were  $\geq 12$  years old. Patients were included if they had one or more diagnoses of idiopathic (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 708.1x; ICD-10-CM code L50.1x), other (ICD-9-CM code 708.8x; *International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM] code L50.8x), or unspecified urticaria (ICD-9-CM code 708.9x; ICD-10-CM code L50.9x), were subsequently initiated on omalizumab (the first administration on or after March 21, 2014, the U.S. Food and Drug Administration approval date), which was indicated for CIU, had no history of omalizumab use before the first visit to AP, and  $\geq 6$  months of data postindex confirmed with a patient visit recorded in the data base.

## Omalizumab Use

Omalizumab use was described during the follow-up period based on administered injections recorded in the EMR. The dosing regimen (*i.e.*, dose and frequency of administration) was described during the first period of continuous omalizumab use (defined below). The change in frequency of administration was defined as an increase or decrease of  $\geq 7$  days of the time between consecutive visits compared with the initial frequency. Discontinuation was defined as a gap of  $\geq 90$  days between consecutive omalizumab

administrations or between the last administration and the end of follow-up. The date of discontinuation was defined as 28 days after the last omalizumab administration that preceded a gap in administrations of  $\geq 90$  days. Reasons for final discontinuation were obtained from the chart abstraction. Restart was defined as an administration of omalizumab after a discontinuation. Duration of continuous use was defined as the time from the first administration to the first discontinuation date or 28 days after the last omalizumab administration if there was no discontinuation.

## Outcomes Associated with Omalizumab Use

Outcomes were measured by using provider assessments (PA) of disease control (well controlled, not well controlled, or unable to determine) and course (improved, same, variable, worse, or unable to determine), and patient-reported symptoms (presence of itching, rash, and swelling). Initial data on PAs were obtained from the structured EMR. For patients with missing information, the data were obtained through chart abstraction: either directly from the chart or entered by a chart abstractor if he or she could assess the disease course and control with confidence based on the information on file; if not enough information was in record, then “unable to determine” was entered as a PA value. Follow-up levels of PAs and symptoms were measured at 6-month intervals and compared with baseline levels in patients with data both at baseline and the follow-up time point. Baseline levels of symptoms were assessed up to 6 months before the index date, and follow-up levels were assessed during each 6-month interval postindex. To define baseline and follow-up levels of PAs, the value closest to the index date  $\leq 12$  months before, and the value closest to the follow-up time point  $\pm 90$  days were selected.

## Sensitivity Analysis

In the sensitivity analysis for PAs of disease control and course, all the values of “unable to determine” were excluded from the data to evaluate if the results remained consistent when considering only definite assessments.

## Statistical Analysis

For the assessment of outcomes, statistical comparisons with baseline were conducted by using univariate generalized estimating equations with adjustment for measurements on the same patients. Binary variables were compared by assuming binomial distribution and a logit link. The results were reported as odds ratios (OR) with 95% confidence intervals (CI). Continuous variables were compared by assuming a normal distribution. The results were reported as mean differ-

ences with 95% CIs. All statistical analyses were conducted by using SAS version 9.4. (SAS Institute, Inc., Cary, NC).

## RESULTS

### Patient Characteristics and Duration of Follow-up

A total of 1096 patients were included and followed up for a mean  $\pm$  standard deviation (SD) of  $19 \pm 10.7$  months, with 65.9, 43.5, and 27.0% of the patients followed up for  $\geq 12$ ,  $\geq 18$ , and  $\geq 24$  months. The mean  $\pm$  SD age was  $44.1 \pm 15.3$  years; 74.4% were women (Table 1). The patients were predominantly white (77.6%), resided in the South (78.5%), and were covered by private health insurance (83.1%). Angioedema was observed in 26.5% of the patients. The mean  $\pm$  SD time to omalizumab initiation was  $230.5 \pm 429.3$  days from the first observed CIU diagnosis. Most of the patients (97.4%) had previous CIU-related treatments, including second-generation H<sub>1</sub>-antihistamines (89.9%) and oral corticosteroids (66.4%).

### Number of Omalizumab Administrations and Dosing Regimen

During follow-up, the patients received a mean  $\pm$  SD of  $15.1 \pm 10.5$  omalizumab administrations (Fig. 1). Most patients (89.7%) initiated omalizumab on a 300-mg dose. Of the 1072 patients with two or more omalizumab administrations, 52.7% had omalizumab administered once every 4 weeks (Fig. 2). Only a fraction of the patients changed dose: 6.3% increased and 12.0% decreased their dose. Although most of the patients maintained the initial dose, only 19.4% maintained the initial frequency of administration (Fig. 3). Most patients (57.5%) decreased the frequency of omalizumab administration at some point during the follow-up.

### Continuous Use, Discontinuation, and Restart

The patients received omalizumab continuously for a mean  $\pm$  SD of  $14.2 \pm 10.6$  months. Among the patients with at least 6, 9, and 12 months of follow-up ( $n = 1069$ ,  $n = 900$ , and  $n = 722$ , respectively), 79.6, 72.3, and 69.1% received omalizumab continuously up to 6, 9, and 12 months, respectively. More than one-third of the patients (38.5%) discontinued omalizumab after a mean  $\pm$  SD of  $8.2 \pm 7.4$  months. Of 422 patients who discontinued omalizumab, information on the reasons for the final discontinuation was available in 100 patients (23.7%). The most commonly reported reason was inefficacy (failure), reported in 25 of those who discontinued omalizumab (5.9%) (Fig. 4). Among patients who discontinued omalizumab, 55.5% restarted omalizumab after a mean  $\pm$  SD of  $5.2 \pm 5.4$  months.

Table 1 Baseline characteristics

|                                                                     | All Patients<br>(N = 1096) |
|---------------------------------------------------------------------|----------------------------|
| Demographics                                                        |                            |
| Age, mean $\pm$ SD, median, y*                                      | $44.12 \pm 15.36$ , 45     |
| Female, n (%)                                                       | 819 (74.7)                 |
| Race, n (%)                                                         |                            |
| White                                                               | 851 (77.6)                 |
| Black or African American                                           | 151 (13.8)                 |
| Asian                                                               | 34 (3.1)                   |
| Other                                                               | 9 (0.8)                    |
| Unknown                                                             | 51 (4.7)                   |
| Region, n (%)                                                       |                            |
| South                                                               | 860 (78.5)                 |
| West                                                                | 119 (10.9)                 |
| Midwest                                                             | 89 (8.1)                   |
| Northeast                                                           | 28 (2.6)                   |
| Year of index date, n (%)                                           |                            |
| 2014                                                                | 133 (12.1)                 |
| 2015                                                                | 230 (21.0)                 |
| 2016                                                                | 347 (31.7)                 |
| 2017                                                                | 386 (35.2)                 |
| Clinical characteristics, n (%)                                     |                            |
| Presence of angioedema#                                             | 290 (26.5)                 |
| Presence of physical urticaria#                                     | 87 (7.9)                   |
| Top-3 CIU-related comorbidities#                                    |                            |
| Allergic rhinitis                                                   | 323 (29.5)                 |
| Asthma                                                              | 133 (12.1)                 |
| Food allergies                                                      | 99 (9.0)                   |
| Previous CIU-related treatment (received and/or prescribed), n (%)§ |                            |
| Any                                                                 | 1065 (97.2)                |
| H <sub>1</sub> -antihistamines, second generation                   | 985 (89.9)                 |
| H <sub>1</sub> -antihistamines, first generation                    | 742 (67.7)                 |
| Oral corticosteroids                                                | 728 (66.4)                 |
| H <sub>2</sub> -antihistamines                                      | 721 (65.8)                 |
| Leukotriene modifiers                                               | 661 (60.3)                 |
| Doxepin                                                             | 154 (14.1)                 |
| Anti-inflammatory agents                                            | 50 (4.6)                   |
| Immunosuppressive agents                                            | 79 (7.2)                   |

SD = Standard deviation; CIU: chronic idiopathic urticaria.

\* Measured at the index date.

# Conditions, identified by using International Classification of Diseases, Ninth Revision, Clinical Modification and International Classification of Diseases, Tenth Revision, Clinical Modification codes, were active on the patient's problem list as of the index date.

§ Based on prescription and chart review data any time before the index date.

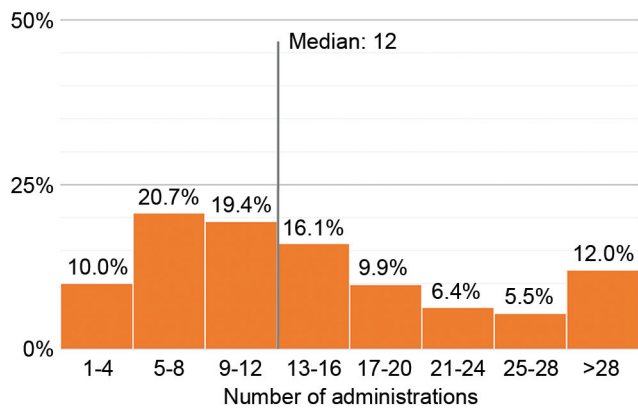


**Figure 1.** Number of omalizumab administrations in patients with CIU (N = 1096).<sup>1</sup> CIU = Chronic idiopathic urticaria. <sup>1</sup>Measured during the follow-up period, which spanned  $\geq 6$  months from the index date until the end of data availability (June 2018) or the last visit to an Allergy Partners clinic.

### Disease Control and Course

The mean (median) time from baseline values of PAs of disease control and course to the index date was 28 days (19 days); among 90% of patients, the time from baseline PAs of disease control and course to index date was  $\leq 67$  days. At month 6 versus baseline, 33.3 versus 1.6% of patients were well controlled; the odds of being well controlled at month 6 were 32 times higher relative to baseline (Fig. 5). At month 12, 42.9% of the patients were well controlled compared with 1.4% at baseline, which reflected 53 times higher odds of being well controlled relative to baseline. The patients had 55 times higher odds of being well controlled at month 18 (52.5%) versus baseline (2.0%), and 46 times higher odds at month 24 (48.3%) versus baseline (2.0%). Higher odds of disease control relative to baseline were sustained beyond 24 months (Fig. 5). Relative to baseline, the patients had 80 to 89% lower odds of not being well controlled between months 6 and 24. This trend continued beyond 24 months.

The patients had 16 times higher odds of improved disease course at month 6 (50.4%) versus baseline (6.1%). Similarly, at month 12 (46.3%) versus baseline (5.7%), month 18 (43.9%) versus baseline (5.2%), and month 24 (37.8%) versus baseline (3.5%), the odds of improved disease course were 14 to 17 times higher (Fig. 6). Relative to baseline, the odds of a worse disease course were 75 to 88% lower between months 6 and 24, with a similar trend beyond 24 months. The odds of the same or a variable disease course during follow-up versus baseline mostly trended down, but statistical significance was rarely reached.

### Patient-Reported Concerns of Symptoms

At month 6 versus baseline, the odds of reporting itching (92.2 versus 96.8%), rash (51.7 versus 64.3%),

and swelling (24.9 versus 42.1%) were 61, 41, and 54% lower (Fig. 7). The trend of improvement continued at month 12 postindex and beyond.

### Sensitivity Analysis

Results of the sensitivity analysis for PAs of the disease control and course were consistent with the main results at all time points.

### DISCUSSION

This real-world study presented long-term outcomes of a large cohort of U.S. patients with CIU who were initiated on omalizumab. The vast majority of the patients were initiated on a 300-mg dose and treated without a dose titration up or down, but often decreased the frequency of administration, for  $> 12$  months on average. Improved CIU control, course, and symptoms were observed, starting at 6 through 24 months after initiation of omalizumab and beyond.

The patient characteristics were comparable with those reported in clinical trials and other real-world studies.<sup>8–10,19</sup> One notable difference was the lower prevalence of angioedema (26.5 versus 38–54% in the clinical trials<sup>8–10</sup> and 33% in another real-world study<sup>19</sup>), which was indicative of a more severe form of CIU and can be considered an unfavorable prognostic factor. In this study, a higher proportion of patients used second-generation H<sub>1</sub>-antihistamines before omalizumab initiation compared with a 2018 claims study (89.9 versus 23.7%).<sup>19</sup> As over-the-counter medications, antihistamines are poorly captured in claims data. Chart abstraction in this study enriched the information with regard to antihistamine use, which may explain higher rates of use observed. Of note, international urticaria treatment guidelines recommend up dosing second-generation H<sub>1</sub>-antihistamines up to fourfold before adding on omalizumab as the third-line therapy.<sup>7</sup>

Although omalizumab use in U.S. patients with CIU has been previously examined with claims data, no large study described its use based on administered injections, which, compared with claims, allowed a more accurate picture of use. In this study, nearly 90% of the patients were initiated and maintained on a 300-mg dose of omalizumab, which demonstrated the best results in controlling CIU symptoms in clinical trials.<sup>20</sup> Although, in some early real-world studies, patients were reported to predominantly start omalizumab on a 150-mg dose, this may reflect a lack of experience with the drug shortly after its approval.<sup>21</sup> Consistent with this study, recent real-world studies reported the majority of patients receiving and maintaining the 300-mg dose.<sup>15,19</sup> In our study, most of the patients adjusted the frequency of administration during the first period of continuous omalizumab use. The

**Figure 2.** Initial omalizumab dosing regimen in patients with CIU. CIU = Chronic idiopathic urticaria. <sup>1</sup>Measured among the patients with CIU with two or more administrations of omalizumab during continuous omalizumab use.

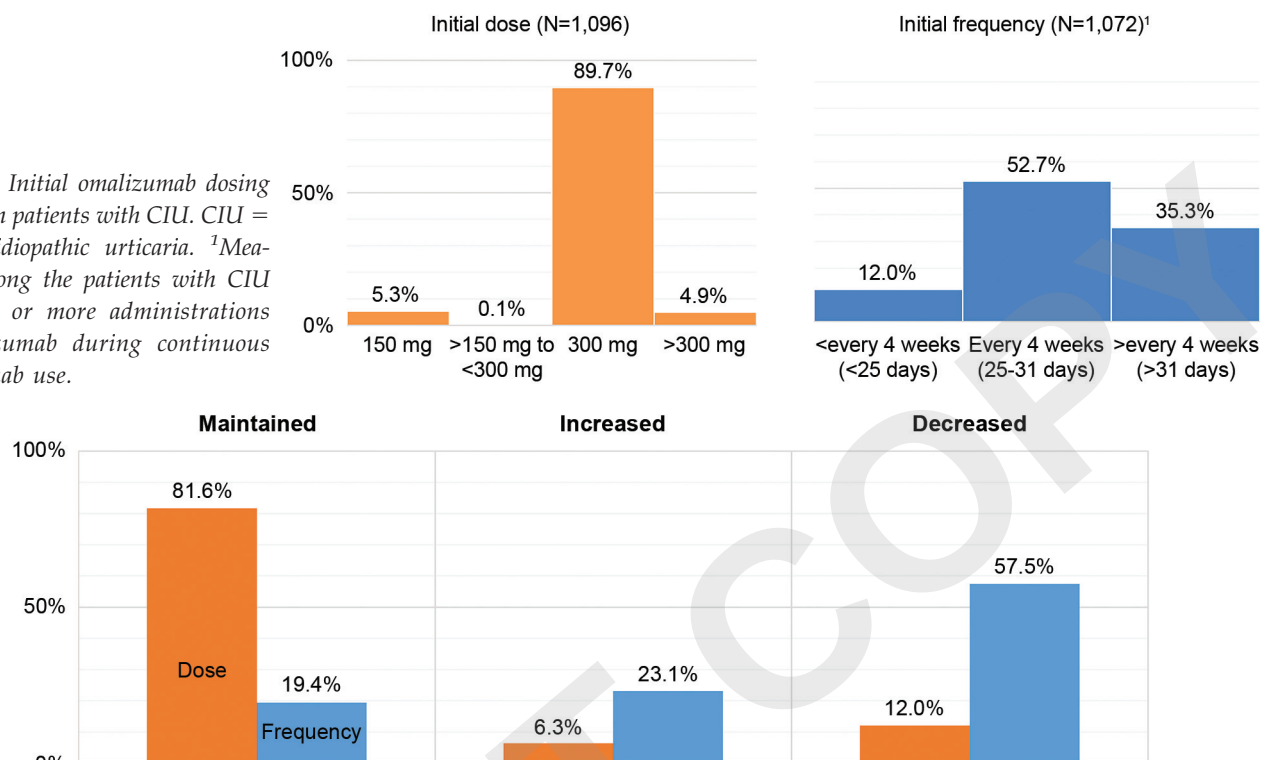


**Figure 3.** Change in omalizumab dosing regimen in patients with CIU (n = 1072).<sup>1</sup> CIU = Chronic idiopathic urticaria. <sup>1</sup>Measured among the patients with CIU and with two or more administrations of omalizumab during continuous omalizumab use; patients with only one administration of omalizumab before discontinuation were included in the “maintained” category. <sup>2</sup>Increase or decrease in frequency of administration was defined as a change of  $\geq 7$  days from the initial frequency of administration.

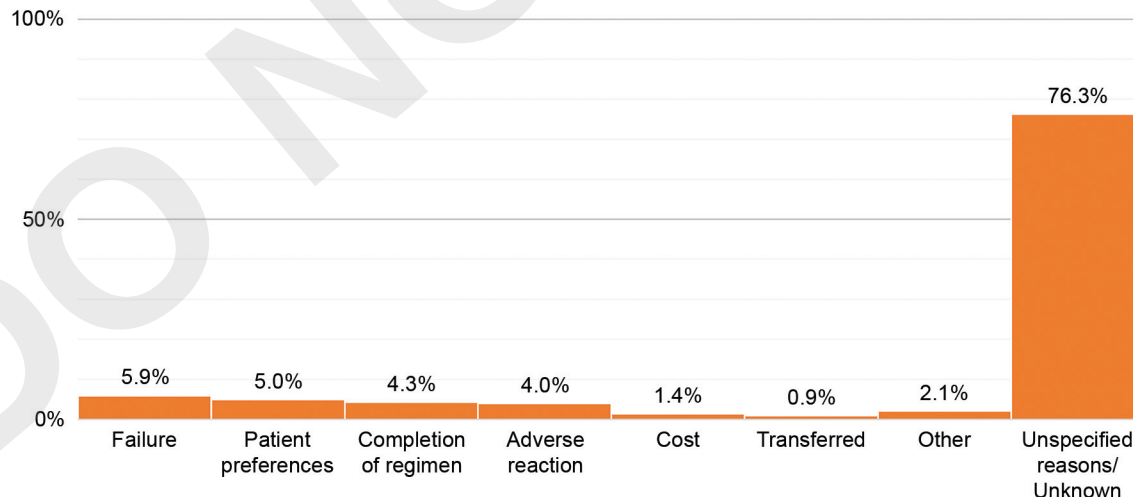


**Figure 4.** Reasons for omalizumab discontinuation in the patients with CIU (n = 422).<sup>1</sup> CIU = Chronic idiopathic urticaria. <sup>1</sup>Reasons for the final discontinuation obtained from chart abstraction and reported among patients with CIU who discontinued omalizumab (n = 422). Discontinuation reason was most often categorized as “other” when omalizumab was stopped due to unrelated medical condition, such as an injury or an operation.

high percentage of patients who increased the intervals between administrations might be indicative of physicians’ attempts to wean patients off omalizumab for a chance of spontaneous remission.<sup>22</sup>

Our results on omalizumab treatment duration and re-initiation after discontinuation parallel evidence

from previous research.<sup>16,19,23</sup> A recent XTEND-CIU (Xolair Treatment Efficacy of LoNger Duration in Chronic Idiopathic Urticaria) trial reported benefits of omalizumab treatment through 12 months, which indicated that patients who remained on the treatment maintained symptom control and experienced

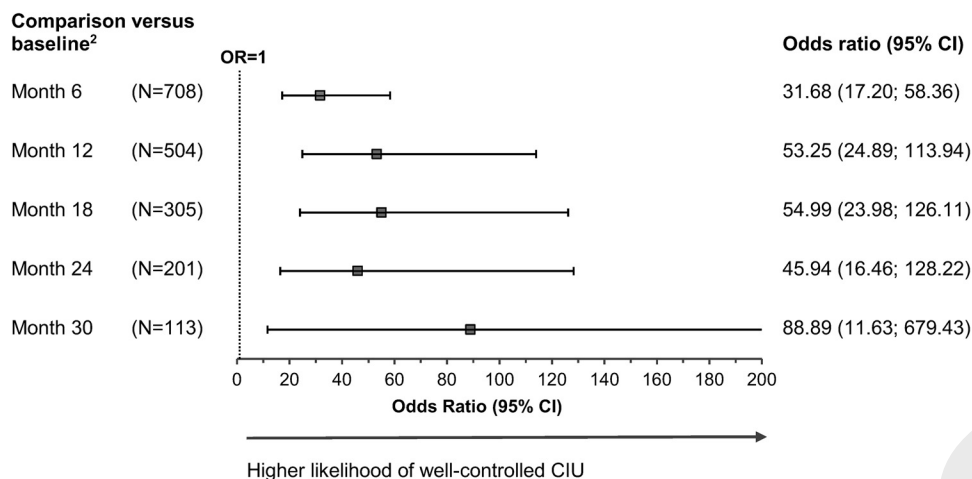


**Figure 5.** Likelihood of well-controlled CIU.<sup>1</sup> CIU = Chronic idiopathic urticaria; CI = confidence interval; OR = odds ratio.<sup>1</sup> Measured based on provider assessment of disease control; assessments observed included “well controlled,” “not well controlled,” and “unable to determine.”<sup>2</sup> Among the patients with one or more measurements at baseline and at time point; comparisons were conducted by using univariate generalized estimating equations with binominal distribution and a logit link.

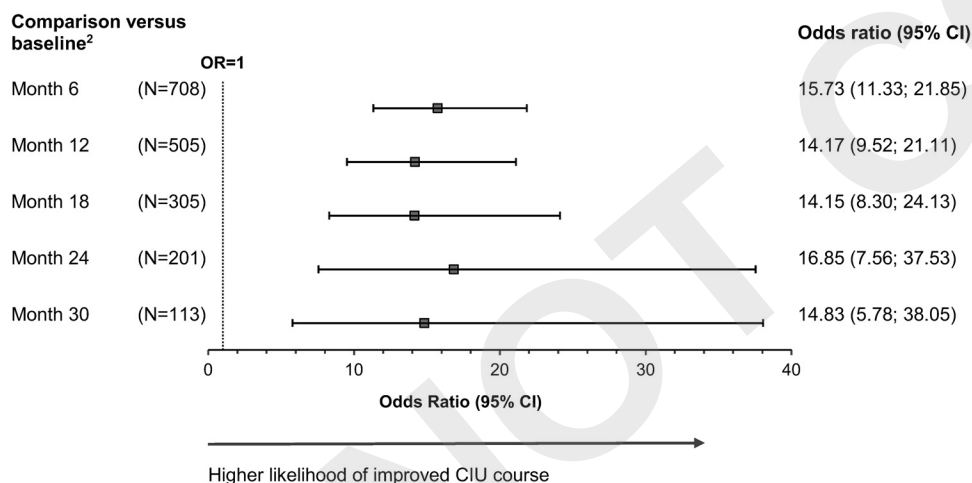


**Figure 6.** Likelihood of improved CIU course.<sup>1</sup> CIU = Chronic idiopathic urticaria; CI = confidence interval; OR = odds ratio.<sup>1</sup> Measured based on provider assessment of disease course; assessments observed included “improved,” “same,” “variable,” “worse,” and “unable to determine.”<sup>2</sup> Among patients with one or more measurements at baseline and at time point; comparisons were conducted by using univariate generalized estimating equations with binominal distribution and a logit link.

fewer angioedema days.<sup>23</sup> In our study, the mean duration of continuous treatment was beyond 12 months. Consistent with recent real-world studies, a large proportion of patients who discontinued omalizumab resumed the treatment.<sup>16,19</sup> The XTEND-CIU study indicates that most patients who discontinue omalizumab experience a relapse but can be safely and effectively re-treated.<sup>23</sup>

In this study, omalizumab treatment was associated with improvements of disease control, course, and symptoms observed at month 6 of omalizumab initiation and continued beyond 24 months. Omalizumab is not a disease-modifying agent. Given that the course of CIU is difficult to predict and varies greatly across patients,<sup>24</sup> and that CIU remission may occur spontaneously within several years of disease onset,<sup>2</sup> it is possible that complete CIU remission in some patients observed in our sample was independent of the use of omalizumab. Nonetheless, this real-world study was useful in providing evidence that omalizumab treatment correlates with relief among patients for whom antihistamines alone failed to control symptoms. A previous real-world study that also used PAs as a

measure of response likewise reported benefits associated with omalizumab use, including a decrease in symptoms after omalizumab initiation.<sup>15</sup> Other large real-world studies on long-term omalizumab outcomes are warranted to confirm these results.

### Study Limitations

Beneficial outcomes were observed at 6 through 24 months after omalizumab initiation and beyond, and there was a signal toward sustained improvement and symptoms remission. This signal must be interpreted with due consideration to the fact that outcomes were assessed in a sample of patients that varied over time (*i.e.*, among patients who had data available at baseline and each of the follow-up time points). Moreover, the study had no control arm due to challenges in identifying patients eligible for but not receiving omalizumab, and unobserved factors (*e.g.*, spontaneous remission of CIU) may have confounded results. Formalized response measures, *e.g.*, the urticaria activity score over 7 days, were not available. PA measures of response used may limit comparability of results with other

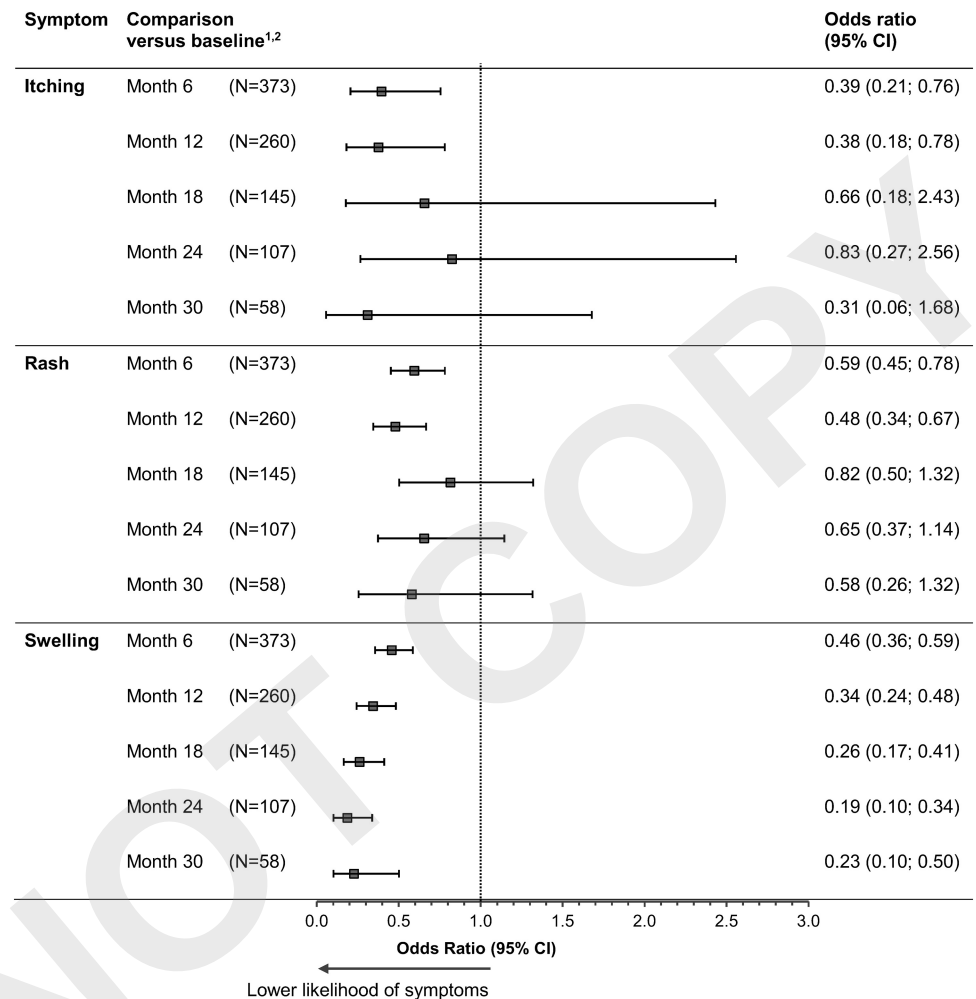


**Figure 7.** Likelihood of patient-reported symptoms. CI = Confidence interval; OR = odds ratio. <sup>1</sup>Among patients with one or more measurements at baseline and at time point; comparisons were conducted by using univariate generalized estimating equations with binominal distribution and a logit link.

studies. Patient-reported symptoms may introduce potential recall bias.

EMR data were not linked to health-care providers outside of the network, and information on additional care and prescriptions was unavailable. With the exception of omalizumab, EMR data contained information on prescriptions ordered rather than dispensed; matched pharmacy claims were not available. In addition, structured EMR data could not fully capture the use of over-the-counter medications (e.g., H<sub>1</sub>-antihistamines), although chart abstraction of information on previous treatments conducted for the study mitigated these limitations to an extent.

Information on reasons for omalizumab discontinuation was scarce. Further studies are needed to elucidate reasons for discontinuation. More than half of the patients in this study were from the South; if important differences exist across regions, results might not be generalizable to other regions. The nature of the data did not allow evaluation of health-care costs associated with the use of omalizumab. Further real-world studies are needed to understand cost implications of omalizumab.

## CONCLUSION

In this large, real-world study of U.S. patients with CIU, most of the patients were initiated on a 300-mg dose of omalizumab and treated without titration up or down for >12 months on average. Patients experienced improved CIU control, course, and symptoms starting at 6 through 24 months after initiation of omalizumab.

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