Background: Few data are available that describe response patterns in patients with chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria (CSU) treated with omalizumab. Objective: We sought to describe response patterns by using data from the 3 pivotal omalizumab CIU/CSU trials. Methods: Every 4 weeks, randomized patients received dosing with placebo or 75, 150, or 300 mg of omalizumab (ASTERIA I: n = 318, 24 weeks; ASTERIA II: n = 322, 12 weeks) or placebo or 300 mg of omalizumab (GLACIAL: n = 335, 24 weeks). Response was defined as well-controlled urticaria (weekly Urticaria Activity Score [UAS7] ≤ 6) or complete response (UAS7 = 0). Results: Response rates were dose dependent and highest with 300 mg of omalizumab. Some patients responded early (before week 4). At week 12, a higher proportion of patients treated with 300 mg of omalizumab reported a UAS7 ≤ 6 (26.0% [75 mg of omalizumab], 40.0% [150 mg of omalizumab], 51.9% [300 mg of omalizumab], and 11.3% [placebo] for ASTERIA I; 26.8% [75 mg of omalizumab], 42.7% [150 mg of omalizumab], 65.8% [300 mg of omalizumab], and 19.0% [placebo] for ASTERIA II; and 52.4% [300 mg of omalizumab] and 12.0% [placebo] for GLACIAL) or a UAS7 = 0 (11.7% [75 mg of omalizumab], 15.0% [150 mg of omalizumab], 35.8% [300 mg of omalizumab], and 8.8% [placebo] for ASTERIA I; 15.9% [75 mg of omalizumab], 22.0% [150 mg of omalizumab], 44.3% [300 mg of omalizumab], and 5.1% [placebo] for ASTERIA II; and 33.7% [300 mg of omalizumab] and 4.8% [placebo] for GLACIAL). In patients receiving 300 mg of omalizumab with 24 weeks of treatment, median time to achieve a UAS7 ≤ 6 was 6 weeks (ASTERIA I and GLACIAL) and median time to achieve a UAS7 = 0 was 12 or 13 weeks (ASTERIA I and GLACIAL, respectively). Some patients who achieved well-controlled urticaria or complete response sustained response throughout the treatment period. Conclusion: Benefits of omalizumab treatment were evident early (before week 4) in some patients and persisted to week 24. Use of 300 mg of omalizumab demonstrated best results in controlling CIU/CSU symptoms. (J Allergy Clin Immunol 2016;137:474-81.)

Key words: Omalizumab, chronic idiopathic urticaria, chronic spontaneous urticaria, responder analysis, complete response, well-controlled urticaria

Chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria (CSU) is a condition characterized by spontaneous appearance of pruritic hives, angioedema, or both that recur without an identifiable external cause and persist for 6 weeks or longer.1-3 CIU/CSU is a rare condition, and its prevalence was reported to range between 0.6% and 0.8% in the general population of Spain and Germany.4,5 Patients with CIU/CSU report substantial worsening of health-related quality of life.6-8

The Urticaria Activity Score (UAS) is a validated measure to assess disease activity in patients with CIU/CSU. The UAS score (range, 0-6) comprises a sum of daily ratings for itch severity and number of hives (0-3 points for each). The weekly Urticaria Activity Score (UAS7) sums UAS scores during a 7-day period, and possible values for the UAS7 range from 0 to 42. US and European guidelines recommended evaluating disease activity and response to treatment in routine clinical practice.2,3 The 2014 CIU/CSU guidelines for the United States and Europe2,3 recommend treating CIU/CSU in a stepwise manner, starting with
monotherapy with a second-generation antihistamine. However, complete response to H1-antihistamines has been reported to reach slightly greater than 50% in patients with CIU/CSU. Although the next steps vary slightly between guidelines, recommendations include increasing the dose of H1-antihistamine up to 4-fold and/or adding other therapies, such as H2-antihistamines or leukotriene receptor antagonists (LTRAs). Should lack of control continue, guidelines recommend using omalizumab.

Data from 3 phase III clinical trials (ASTERIA I, ASTERIA II, and GLACIAL) demonstrated the efficacy and safety of omalizumab to treat patients with CIU/CSU. Despite the positive results of these trials, many clinical questions remain regarding the response to omalizumab in patients with CIU/CSU. The expected timing of response to omalizumab has not been previously reported. Furthermore, published data do not provide guidance on how many doses might be needed to define response or lack of response.

The aim of this analysis was to investigate response patterns of omalizumab to treat CIU/CSU in the phase III clinical trial data, with a goal of providing a practical approach to omalizumab use for clinicians by using omalizumab in the real-world setting.

**METHODS**

**Phase III omalizumab studies**

ASTERIA I, ASTERIA II, and GLACIAL were phase III, global, randomized, multicenter, double-blind, placebo-controlled clinical trials designed to assess the efficacy and safety of omalizumab use in patients with CIU/CSU.

ASTERIA I and ASTERIA II enrolled patients with CIU/CSU who remained symptomatic despite treatment with H1-antihistamines at approved doses. Enrolled patients in both studies had to have a UAS7 > 16 (equivalent to 4-fold and/or adding other therapies, such as H2-antihistamines or leukotriene receptor antagonists (LTRAs). Should lack of control continue, guidelines recommend using omalizumab.

Data from 3 phase III clinical trials (ASTERIA I, ASTERIA II, and GLACIAL) demonstrated the efficacy and safety of omalizumab to treat patients with CIU/CSU. Despite the positive results of these trials, many clinical questions remain regarding the response to omalizumab in patients with CIU/CSU. The expected timing of response to omalizumab has not been previously reported. Furthermore, published data do not provide guidance on how many doses might be needed to define response or lack of response.

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**TABLE I. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ASTERIA I (n = 318)</th>
<th>ASTERIA II (n = 322)</th>
<th>GLACIAL (n = 335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>41.2 (14.5)</td>
<td>42.5 (13.7)</td>
<td>43.1 (14.1)</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>231 (72.6)</td>
<td>244 (75.8)</td>
<td>241 (71.9)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>263 (82.7)</td>
<td>272 (84.5)</td>
<td>298 (89.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>14 (4.4)</td>
<td>9 (2.8)</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>Black</td>
<td>33 (10.4)</td>
<td>28 (8.7)</td>
<td>21 (6.3)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (2.5)</td>
<td>13 (4.0)</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>82.2 (21.0)</td>
<td>82.4 (21.9)</td>
<td>83.9 (22.5)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>29.3 (6.8)</td>
<td>29.8 (7.3)</td>
<td>29.8 (7.8)</td>
</tr>
<tr>
<td>Duration of CIU (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (&gt;10)</td>
<td>80 (25.2)</td>
<td>94 (29.3)</td>
<td>103 (30.9)</td>
</tr>
<tr>
<td>Negative (&lt;10)</td>
<td>237 (74.8)</td>
<td>227 (70.7)</td>
<td>230 (69.1)</td>
</tr>
<tr>
<td>Total IgE level (UI/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>182.8 (387.8)</td>
<td>168.2 (231.9)</td>
<td>158.5 (287.7)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>83 (1-5000)</td>
<td>78 (1-1450)</td>
<td>78 (1-3050)</td>
</tr>
<tr>
<td>Presence of angioedema at baseline (%)</td>
<td>151 (47.5)</td>
<td>131 (40.7)</td>
<td>178 (53.1)</td>
</tr>
</tbody>
</table>

**Abbreviations used**

CIU: Chronic idiopathic urticaria
CSU: Chronic spontaneous urticaria
LTRAs: Leukotriene receptor antagonist
UAS: Urticaria Activity Score
UAS7: Weekly Urticaria Activity Score

**Data collection and assessments**

Patients used an electronic handheld device (eDiary) to record data twice daily for the validated Urticaria Patient Daily Diary. These data informed the GLACIAL study design have been published by Kaplan et al.

All 3 studies were conducted in accordance with US Food and Drug Administration regulations, the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and any other applicable laws. Institutional review board approval and informed consent were obtained from all patients. These trials are registered with ClinicalTrials.gov (no. NCT01287117 for ASTERIA I, no. NCT01292473 for ASTERIA II, and no. NCT01264939 for GLACIAL).
We calculated the percentage of patients who achieved responses at time points separated by 4-week increments, as well as the percentage of non-responders at 12 weeks who responded by week 24. We computed the proportion of weeks in the active treatment period during which patients experienced their responses; this analysis was performed for all patients. We estimated the percentage of patients who achieved a response they later sustained through the end of the drug administration period. The χ² test was used to compare all percentages in the conducted analyses. Median time to achieve first response was calculated using the Kaplan-Meier method; time to achieve first response was compared between treatment groups by using the log-rank test. All statistics were calculated with SAS 9.2 software.

![Graphs showing percentage of responders by 4-week increments for different conditions.](image)

**Analyses**

FIG 1. Percentage of responders by 4-week increments. **A,** ASTERIA I UAS7 ≤ 6; **B,** ASTERIA I UAS7 = 0; **C,** ASTERIA II UAS7 ≤ 6; **D,** ASTERIA II UAS7 = 0; **E,** GLACIAL UAS7 ≤ 6; and **F,** GLACIAL UAS7 = 0.

*P < .05 and **P < .001. OMA, Omalizumab.
Institute, Cary, NC). Missing UAS7 data at week 12 resulted in patients imputed as nonresponders.

RESULTS
Patient demographics
In the following 3 phase III studies of omalizumab in patients with CIU/CSU, a total of 975 patients were randomized and received at least 1 dose of study drug: ASTERIA I (75 mg of omalizumab [n = 77], 150 mg of omalizumab [n = 80], 300 mg of omalizumab [n = 81], and placebo [n = 80]); ASTERIA II (75 mg of omalizumab [n = 82], 150 mg of omalizumab [n = 82], 300 mg of omalizumab [n = 79], and placebo [n = 79]); and GLACIAL (300 mg of omalizumab [n = 252] and placebo [n = 83]). Baseline patient characteristics in the studies were similar (Table I).9-11 Most of the patients in each study were white, and the majority were female. The average age ranged from 41.2 years (ASTERIA I) to 43.1 years (GLACIAL), and the baseline Chronic Urticaria Index was negative (<10) for most patients (69% [GLACIAL] to 75% [ASTERIA I]). Patients’ baseline characteristic data have been published elsewhere.9-11

Responders
Response at different time points. At week 4, after a single dose of study drug, well-controlled urticaria (UAS7 ≤ 6) was reported by 5%, 12%, 21%, and 37% of patients in ASTERIA I (placebo and 75, 150, or 300 mg of omalizumab, respectively); 13%, 15%, 28%, and 51% of patients in ASTERIA II (placebo and 75, 150, or 300 mg of omalizumab, respectively); and 2% and 37% of patients in GLACIAL (placebo and 300 mg of omalizumab, respectively). At week 4, a complete response (UAS7 = 0) was noted in 1%, 5%, 6%, and 19% of patients in ASTERIA I (placebo and 75, 150, or 300 mg of omalizumab, respectively); 0%, 4%, 6%, and 24% of patients in ASTERIA II (placebo and 75, 150, or 300 mg of omalizumab, respectively); and 0% and 15% of patients in GLACIAL (placebo and 300 mg of omalizumab, respectively). The percentage of well-controlled urticaria (UAS7 ≤ 6) and complete responders (UAS7 = 0) during the active treatment period increased with continued dosing (Fig 1). The 300-mg dose of omalizumab produced the highest response rates among all study arms.

Patients in ASTERIA I and GLACIAL continued to receive therapy beyond week 12. With continued dosing, some patients who had not met the definitions of response at week 12 met those definitions at week 24: ASTERIA I (45.7%, 34.4%, and 58.1%, respectively, of the 75-, 150-, and 300-mg arms and 38.2% of the placebo arm) and GLACIAL (48.9% in the 300-mg omalizumab arm and 14.3% in the placebo arm; Fig 2).

Median time to achieve response. Of 12 weeks of active treatment (ASTERIA II), the median time to achieve well-controlled urticaria (UAS7 ≤ 6) was 8, 7, and 3 weeks (75, 150, and 300 mg of omalizumab, respectively); fewer than 50% of placebo patients achieved a UAS7 ≤ 6 within the first 12 weeks of active treatment, and therefore a median time to the end point could not be calculated. In the same study, median time to achieve complete response (UAS7 = 0) was 8 weeks for patients receiving 300 mg of omalizumab; fewer than 50% of patients in other treatment arms achieved a UAS7 = 0 within the 12-week period.

Of 24 weeks of treatment, the median time to achieve well-controlled urticaria (UAS7 ≤ 6) was 11 and 6 weeks (150 and 300 mg of omalizumab, respectively; ASTERIA I) and 6 weeks (300 mg of omalizumab, GLACIAL; Fig 3); in other treatment arms, fewer than 50% of patients achieved the outcome by week 24. The median time to achieve complete response (UAS7 = 0) was 12 and 13 weeks (300 mg of omalizumab; ASTERIA I and GLACIAL, respectively; Fig 3); in other treatment arms fewer than 50% of patients achieved the outcome by week 24. Of the patients being treated with 300 mg of omalizumab who had not achieved well-controlled urticaria (UAS7 ≤ 6) as of week 12, 58% achieved it between weeks 13 and 24. In contrast, of the patients receiving placebo who had not achieved well-controlled urticaria as of week 12, 38% achieved it between weeks 13 and 24.

Length of response. The proportion of weeks in the active treatment (the first 12 weeks in ASTERIA II and the first 24 weeks in ASTERIA I and GLACIAL) period during which patients experienced response was highest in the 300-mg omalizumab treatment arm (Fig 4). To calculate this outcome, we summed the total number of weeks during which patients reported a response and divided it by the total number of patient-weeks in the arm. This effect was consistent in all 3 studies.

Sustained response. Sustained response was defined as instances when patients who achieved well-controlled urticaria (UAS7 ≤ 6) or complete response (UAS7 = 0) maintained that response through the rest of the active treatment period (week 12 [ASTERIA II] and week 24 [ASTERIA I and GLACIAL]; Fig 5). In the 300-mg omalizumab arms, more patients achieved sustained responses and did so earlier than patients in other treatment arms.

DISCUSSION
The results of this study illustrate the response patterns of patients with CIU/CSU treated with omalizumab. Complete
response (UAS7 = 0) and achievement of well-controlled urticaria (UAS7 ≤ 6) appeared early (before week 4) in some patients, and some patients continued to achieve response up to week 24. Some patients responded to treatment after the first injection; however, others took longer to respond. Indeed, the fact that some patients responded after week 12 suggests that stopping injection; however, others took longer to respond. Indeed, the fact that some patients responded after week 12 suggests that stopping
Our findings of a subpopulation of patients with CIU/CSU with a late response to omalizumab concur with data published by Uysal et al.19 The authors individualized omalizumab doses and dosing intervals to treat patients with different types of urticaria: CIU/CSU (85%), delayed pressure urticaria (22%), urticaria factitia (11%), contact urticaria (7%), and heat contact urticaria (7%).19 This small single-arm open-label study included 27 patients with urticaria (aged 10-65 years) who were started on 150 mg of omalizumab. In 2 weeks, physicians evaluated each patient’s condition and prescribed the next dose based on how the patient responded. Approximately 56% (15/27) of patients reached a UAS > 2 after a single 150-mg omalizumab dose and stayed in this dose category, and the remaining patients (12/27) received 300 mg of omalizumab at week 3 and remained in this dose category.

In the “time to response” analyses, after week 12, the Kaplan-Meier curves of the placebo and 300-mg omalizumab groups demonstrated apparently similar slopes. By week 12, many of the patients in the 300-mg omalizumab group had already achieved a response (well-controlled urticaria or complete response). Therefore, the group had begun to reach a ceiling beyond which further improvement was difficult. This was most noticeable in the patients who achieved well-controlled urticaria (UAS7 ≤ 6). However, when examining only patients who had an opportunity for improvement, we see that the percentage of patients who had not achieved a UAS7 ≤ 6 at week 12 but responded as such during weeks 13 to 24 was 58% in the 300-mg omalizumab group and 38% in the placebo group. The study was not powered to detect this end point of improvement after 12 weeks among patients not yet achieving response, and statistical tests comparing such end points were not performed among this small sample; thus we are not able to draw any strong conclusions regarding later responses to omalizumab.

Although the definitions of response were prespecified outcomes in ASTERIA I and II and GLACIAL,9-11 the authors are not aware of any formal definition of response to treatment (with any medication) for patients with CIU/CSU. The state of well-controlled urticaria (UAS7 ≤ 6) is a reasonable and clinically relevant threshold because it requires patients to be well-controlled with only minimal symptoms. Complete response (UAS7 = 0), which connotes complete elimination of itch and hives, stands out as an attractive clinical objective but is often difficult to achieve. Regardless of the responder definition, the 300-mg dose of omalizumab demonstrated the best outcomes. Therefore, it might be reasonable to initiate treatment with the 300-mg dose to ensure best outcomes for the patients.

Data from this analysis might inform decisions regarding an approach to evaluating response to omalizumab treatment. Knowledge of expected response to omalizumab therapy might assist prescribers in determining the length of a therapeutic trial and inform patients or prescribers as to what to expect from omalizumab therapy. Setting patients’ expectations regarding the risks and benefits of a therapy can improve adherence to a treatment regimen and contribute to optimization of outcomes.20

Continued investigation into time to response, identification of specific phenotypes in response to omalizumab, and length of treatment will be important to prescribers who have patients who require omalizumab for management of CIU/CSU. Improving our understanding of the activity of omalizumab in the inflammatory process associated with symptomatic CIU/CSU and recognizing that a subset of patients might have a delay in response could also
help to inform decisions regarding optimization of omalizumab therapy.

Although phase III, randomized, double-blind, placebo-controlled trials remain the gold standard for establishing efficacy, the results of this analysis should be interpreted in light of its limitations. Clinical trial data were not available beyond week 24, and therefore information on the response to treatment beyond this time is unknown. Results from a phase II dose-ranging study
provided the framework for the flat dosing (non-IgE and non–weight-based dosing) and 4-week interval used in the pivotal studies.21 Despite evidence from the phase II and 3 phase III proof-of-concept studies,9–11 it must be acknowledged that we still have much to learn about optimal dosing of omalizumab in patients with CIU/CSU. On the basis of Genentech’s data on file, we also know that the patients in the placebo arm used more background therapy than patients in the omalizumab arm. Therefore, such misbalance is likely to have unfavorably affected omalizumab arms, as opposed to the placebo arm. In addition, these studies permitted the use of rescue medication (diphenhydramine), and our analysis did not control for rescue medication use. Finally, the comparison arm of these studies included placebo plus standard of care and thus was not a pure untreated placebo arm.

Although this study highlighted 2 categories of responders (ie, early and late) the exact mechanisms responsible for these responses are not completely clear. In addition, some patients experienced relapse of their symptoms during either the treatment or follow-up periods. Understanding patterns in relapses might help physicians effectively dose omalizumab in their practice, although relapse analysis was outside the scope of this study. Further research is needed to understand characteristics predictive of early versus late response, as well as relapse patterns in patients with CIU/CSU treated with omalizumab.

In summary, response patterns to treatment of CIU/CSU with omalizumab were dose dependent; use of the 300-mg dose of omalizumab resulted in the largest percentage of patients who achieved a complete response (UAS7 = 0) or well-controlled urticaria (UAS7 ≤ 6). Half of the patients treated with 300 mg of omalizumab had well-controlled symptoms after 2 injections (median time to response, 6 weeks). The benefits of omalizumab treatment in patients with CIU/CSU were evident to week 24. These data highlight the likelihood of response to omalizumab in patients with CIU/CSU at different time points and will help prescribers set patients’ expectations for therapy.

We thank the clinical trial investigators, staff, and patients who participated in the studies. Medical writing support was provided by Linda Wagner, PharmD, of Excel Scientific Solutions and funded by Genentech, Inc and Novartis Pharmaceuticals Corporation.

Clinical implications: In patients with CIU/CSU, response to omalizumab was dose dependent; treatment with 300 mg of omalizumab resulted in earlier response (before week 4), and response was sustained to week 24.

REFERENCES