ORIGINAL ARTICLE

Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

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ABSTRACT

BACKGROUND

Many patients with chronic idiopathic urticaria (also called chronic spontaneous urticaria) do not have a response to therapy with H_1-antihistamines, even at high doses. In phase 2 trials, omalizumab, an anti-IgE monoclonal antibody that targets IgE and affects mast-cell and basophil function, has shown efficacy in such patients.

METHODS

In this phase 3, multicenter, randomized, double-blind study, we evaluated the efficacy and safety of omalizumab in patients with moderate-to-severe chronic idiopathic urticaria who remained symptomatic despite H_1-antihistamine therapy (licensed doses). We randomly assigned 323 patients to receive three subcutaneous injections, spaced 4 weeks apart, of omalizumab at doses of 75 mg, 150 mg, or 300 mg or placebo, followed by a 16-week observation period. The primary efficacy outcome was the change from baseline in a weekly itch-severity score (ranging from 0 to 21, with higher scores indicating more severe itching).

RESULTS

The baseline weekly itch-severity score was approximately 14 in all four study groups. At week 12, the mean (±SD) change from baseline in the weekly itch-severity score was −5.1±5.6 in the placebo group, −5.9±6.5 in the 75-mg group ($P=0.46$), −8.1±6.4 in the 150-mg group ($P=0.001$), and −9.8±6.0 in the 300-mg group ($P<0.001$). Most prespecified secondary outcomes at week 12 showed similar dose-dependent effects. The frequency of adverse events was similar across groups. The frequency of serious adverse events was low, although the rate was higher in the 300-mg group (6%) than in the placebo group (3%) or in either the 75-mg or 150-mg group (1% for each).

CONCLUSIONS

Omalizumab diminished clinical symptoms and signs of chronic idiopathic urticaria in patients who had remained symptomatic despite the use of approved doses of H_1-antihistamines. (Funded by Genentech and Novartis Pharma; ClinicalTrials.gov number, NCT01292473.)

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Chronic idiopathic urticaria (also called chronic spontaneous urticaria) is defined as itchy hives that last for at least 6 weeks, with or without angioedema, and that have no apparent external trigger.[1] The condition generally has a prolonged duration of 1 to 5 years (persisting for >5 years in 11 to 14% of patients[2,3]) and has a detrimental effect on patients' emotional and physical health-related quality of life.[4,5] The impairment accompanying this disorder has been likened to that seen in patients with ischemic heart disease, with patients feeling a similar lack of energy, social isolation, and emotional upset as those with heart disease.[6] Nonsedating H_1-antihistamines are the current mainstay for initial treatment and are the only agents licensed for use in patients with chronic idiopathic urticaria.[4,7] However, a majority of patients do not have a response to H_1-antihistamines, even when the drugs are administered at three to four times their licensed dose.[4,8-10]

Treatment options for patients who do not have a response to H_1-antihistamines include the use of H_2-antihistamines, leukotriene-receptor antagonists, systemic glucocorticoids, cyclosporine, hydroxychloroquine, dapsone, methotrexate, sulfasalazine, and intravenous immune globulin.[11] None of these agents have yet received regulatory approval for the treatment of chronic idiopathic urticaria. In addition, the data supporting the use of these drugs are limited, and long-term use of some of the agents can be associated with substantial side effects.[11]

Histamine release from cutaneous mast cells has long been associated with the pathogenesis of urticaria, whereas in patients with chronic idiopathic urticaria, basophils and IgE may also play an important role.[12] Omalizumab, a recombinant humanized monoclonal antibody approved as add-on therapy for moderate-to-severe persistent allergic asthma,[13,14] reduces the levels of free IgE and the high-affinity receptor for the Fc region of IgE (FcεRI), both of which are essential in mast-cell and basophil activation.[15,16] Studies have shown that omalizumab may suppress allergen-mediated skin reactions through its reduction of FcεRI function in basophils and mast cells.[15,17] Initial evidence from two proof-of-concept studies showed that omalizumab may be effective in patients with chronic idiopathic urticaria who remained symptomatic despite antihistamine treatment.[18,19] Subsequent data from two phase 2, randomized, placebo-controlled multicenter studies involving a total of 139 patients corroborated these early findings, demonstrating that omalizumab, which has a known safety profile, has beneficial effects on symptoms in patients with chronic idiopathic urticaria who remain symptomatic despite the use of approved doses of H_1-antihistamines.[20,21]

Here we report the results of the first of three phase 3 clinical trials in patients with chronic idiopathic urticaria in which we evaluated the effects of three doses of omalizumab as compared with placebo.

METHODS

STUDY DESIGN

In this international, multicenter, randomized, double-blind, placebo-controlled study, we investigated the efficacy and safety of omalizumab over 28 weeks in adult and adolescent (≥12 years) patients with chronic idiopathic urticaria who had remained symptomatic despite the use of approved doses of H_1-antihistamines. After a 2-week screening period, patients were randomly assigned to four groups in a 1:1:1:1 ratio to receive three subcutaneous injections of omalizumab (at doses of 75 mg, 150 mg, or 300 mg) or placebo.

We selected the doses for this study on the basis of the results of a previous phase 2 dose-ranging study.[20] Doses were administered at 4-week intervals, and to ensure that the blinding was maintained, each dose was administered by a qualified designated clinician who was not involved in the evaluation of the patient's symptoms. This 12-week treatment period was followed by a 16-week follow-up period (for further details, see the Supplementary Appendix, available with the full text of this article at NEJM .org). Patients used an electronic handheld device to self-record data with a validated Urticaria Patient Daily Diary (UPDD)[22,23] (see the Supplementary Appendix). This electronic diary was stamped with the time and date to ensure that data were not included outside of each assessment period.

Patients continued to receive stable doses of their prerandomization H_1-antihistamine throughout the treatment period. During the follow-up period, patients were permitted to use a licensed dose of one additional H_1-antihistamine. For the duration of the study, all patients were provided with diphenhydramine (25 mg) as rescue medication for itch relief (up to a maximum of three doses in 24 hours on the basis of local regulations).

The study protocol, which is available at NEJM.org, was approved by the institutional review board or ethics committee at each study center or by a central institutional review board. The study was conducted in accordance with Food and Drug Administration regulations, Good Clinical Practice guidelines, and any other applicable laws of other countries. An independent data and safety monitoring committee oversaw the study conduct and reviewed blinded and unblinded safety data every 6 months (see the Supplementary Appendix).

STUDY OVERSIGHT

The study was sponsored by Genentech and Novartis Pharma, whose representatives were involved in data collection (along with the investigators) and in the interpretation and analysis of the data and who vouch for the accuracy and completeness of the data presented and for the fidelity of this report to the study protocol. Representatives of both companies were involved in the design of the study, with scientific advice obtained from external experts on chronic idiopathic urticaria. The authors wrote all drafts of the manuscript and made the decision to submit the manuscript for publication. Editorial support and assistance with incorporation of revisions was provided by a medical writer who was employed by Genentech. All authors and contributors were under nondisclosure agreements with Genentech.

PATIENTS

Patients were included in the study if they were between the ages of 12 and 75 years (between 18 and 75 years in Germany) and met all the following criteria: a history of at least 6 months of chronic idiopathic urticaria, the presence of hives associated with itching for at least 8 consecutive weeks at any time before enrollment despite current use of H_1-antihistamines, an urticaria activity score (UAS) during a 7-day period (UAS7) of 16 or more (on a scale ranging from 0 to 42, with higher scores indicating greater activity and a minimally important difference [MID] of 9.5 to 10.5),[24] a weekly itch-severity score of 8 or more (on a scale ranging from 0 to 21, with higher scores indicating more severe itching and an MID of ≥5) during the 7 days before randomization (week 0), a score of 4 or more on the UAS (ranging from 0 to 6, with higher scores indicating greater activity) as assessed by a clinician on at least one of the screening-visit days, and receipt of a licensed dose of a second-generation H_1-antihistamine (see the Supplementary Appendix) for chronic idiopathic urticaria for at least 3 consecutive days immediately preceding the screening visit 14 days before randomization, and no missing electronic-diary entries for the 7 days before randomization.

Exclusion criteria included a clearly defined underlying cause for chronic urticaria (e.g., physical urticaria), routine administration (i.e., daily or every other day for ≥5 consecutive days) of systemic glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or intravenous immune globulin within the previous 30 days for any indication, the use of any H_2-antihistamine or leukotriene-receptor antagonist within 7 days preceding the screening visit 14 days before randomization, the use of H_1-antihistamines at greater-than-licensed doses within 3 days preceding the screening visit 14 days before randomization, a history of cancer, a weight of less than 20 kg, a known hypersensitivity to omalizumab, treatment with omalizumab within the previous year, or pregnancy.

Before inclusion in the study, all patients or a parent or legal guardian (for those under the age of 18 years) provided written informed consent.

ASSESSMENTS

Patients recorded their outcomes in the electronic diary,[22,23] reporting every morning and evening the itch-severity score (with 0 indicating none, 1 indicating mild, 2 indicating moderate, and 3 indicating severe), the number of hives (with 0 indicating none, 1 indicating 1 to 6, 2 indicating 7 to 12, and 3 indicating >12, with an MID of 5.0 to 5.5 for the weekly average), and scores for the size of the largest hive (with 0 indicating none, 1 indicating <1.25 cm, 2 indicating 1.25 to 2.5 cm, and 3 indicating >2.5 cm, with an MID of 4.5 to 5 for the weekly average). The patients reported

once daily on interference with sleep and daily activities (on a scale of 0 to 3, with higher scores indicating more interference on each measure), use of rescue medication as provided in 25-mg diphenhydramine tablets (0 to 9 tablets), the presence of angioedema (yes or no), angioedema management, and any contact with a health care provider (see the Supplementary Appendix for further details). Compliance with reporting in the electronic diary was evaluated throughout the study.

Average daily scores (morning and evening assessments) for itch severity and the number of hives were totaled each week to derive the UAS7.[24] Patients completed the Dermatology Life Quality Index (ranging from 0 to 30, with higher scores indicating a worse quality of life and an MID of 2.24 to 3.10)[25,26] at baseline and at weeks 4, 12, and 28, and the Chronic Urticaria Quality-of-Life Questionnaire (ranging from 0 to 100, with higher scores indicating a worse quality of life) at baseline and at weeks 12 and 28.

STUDY END POINTS

The primary end point was the change from baseline to week 12 in the weekly itch-severity scores. The 12-week score was calculated as the sum of the averaged daily itch-severity score for the previous 7 days, and the baseline score was the sum of the daily itch-severity scores during the 7 days before randomization.

Secondary end points, which were all evaluated at week 12, were changes from baseline in the UAS7 and in the score for the weekly number of hives,[24] the time until a reduction from baseline of at least 5 points[23] in the weekly itch-severity score (the MID), the proportions of patients with a UAS7 of 6 or less (considered to represent improvement in disease), the number of patients with a weekly MID response in the itch-severity score, the change from baseline in the score for the size of the largest hive,[24] the change from baseline in the overall score on the Dermatology Life Quality Index, and the proportion of angioedema-free days from week 4 to week 12 (see the Supplementary Appendix for further details).

We conducted post hoc analyses of the proportion of patients who were free of hives or free of both hives and itching at week 12 (with the latter indicated by a UAS7 of 0) and 13 additional prespecified subgroup analyses for the primary end point. We assessed as exploratory end points changes from baseline in the use of rescue medication (diphenhydramine) and in the score on the Chronic Urticaria Quality-of-Life Questionnaire.

Safety was evaluated by recording and monitoring the frequency and severity of treatment-emergent adverse events and serious adverse events. Verbatim descriptions of adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities* (version 15.0) and analyzed with the use of appropriate thesaurus terms.

STATISTICAL ANALYSIS

In estimating the power for determining efficacy, we assumed a mean change from baseline to week 12 in the weekly itch-severity score of 9 points in the omalizumab group and a mean change of 3.5 points in the placebo group, with a common standard deviation of 6 points. Assuming an early discontinuation rate of 15% by week 12, we determined that the enrollment of 300 patients (75 patients in each treatment group) would yield a power of approximately 98% to detect a difference in treatment effect in the primary end point at the 0.05 level for any omalizumab group.

The efficacy analyses were conducted on the basis of data from the modified intention-to-treat population, which included all patients who had undergone randomization and who had received at least one dose of a study drug. The treatment group was defined according to the treatment the patient was assigned to receive, whereas the safety population was defined according to treatment actually received.

For the primary end point, we analyzed differences between each of the omalizumab treatment groups and the placebo group using an analysis-of-covariance model stratified according to the estimated baseline weekly itch-severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg). The strata were predefined on the basis of the medians reported in a phase 2 clinical study.[20] Missing data at week 12 were imputed with the baseline score (baseline observation carried forward). (Additional details on the statistical methods, including analyses of the secondary end points, are provided in the Supplementary Appendix.)

RESULTS

STUDY POPULATION

Of 466 patients who underwent screening, 146 were excluded and 3 were rescreened. The most

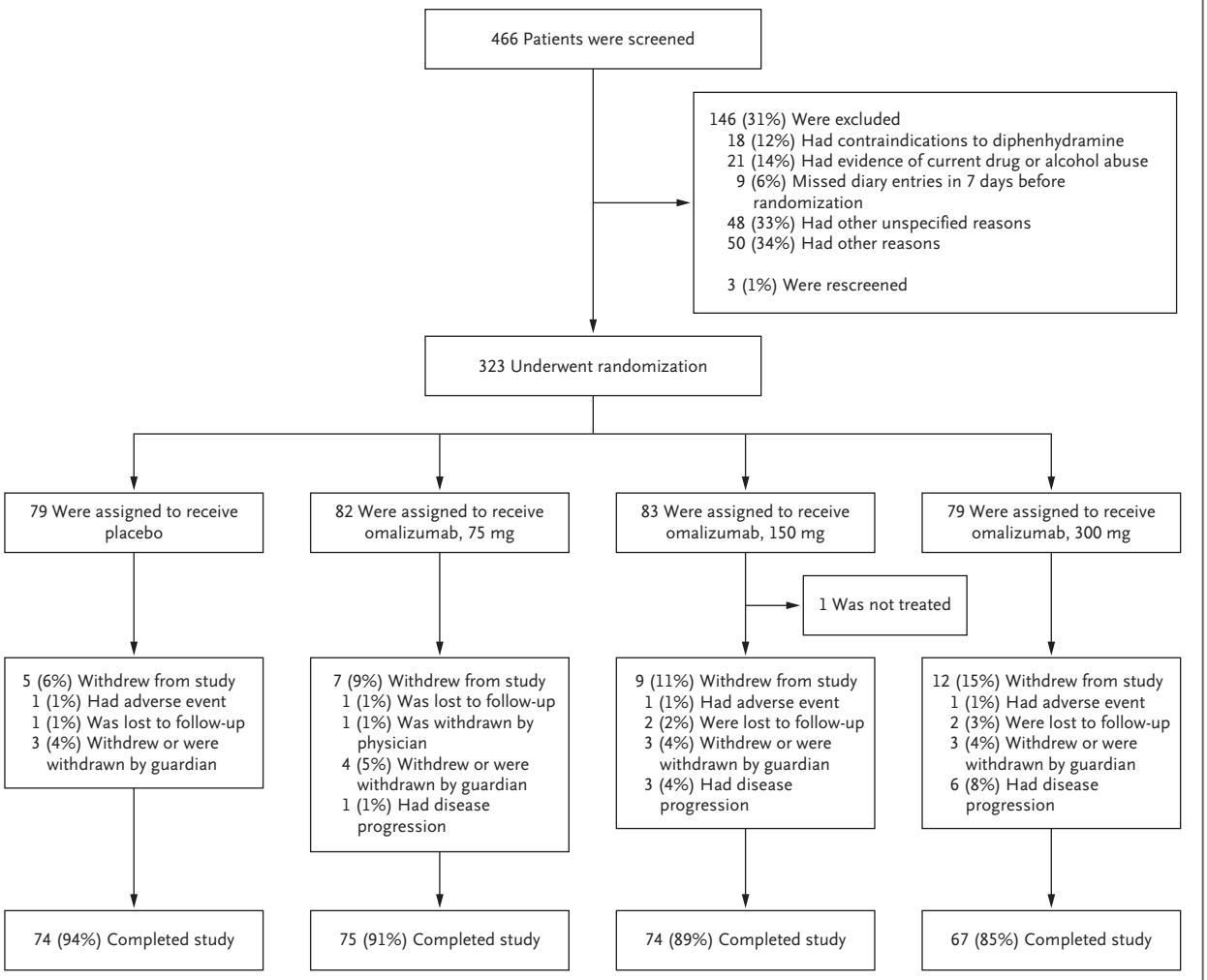

Figure 1. Enrollment and Outcomes.

Among the 83 patients who were assigned to receive 150 mg of omalizumab, 1 patient decided not to receive the study medication and was therefore not included in the modified intention-to-treat population. Six patients who were assigned to receive 75 mg of omalizumab received at least 1 dose of 150 mg of omalizumab during the treatment period and were included in the group receiving 150 mg of omalizumab for the safety analysis.

frequent reasons for exclusion were evidence of current drug or alcohol abuse (14%), contraindications to the use of diphenhydramine (12%), and other reasons that were not specified (33%). Thus, 323 patients underwent randomization and received at least one dose of a study drug in addition to stable doses of their prerandomization H_1-antihistamine (Fig. 1). The overall treatment discontinuation rate was 6%, and the overall study discontinuation rate was 10%, with no major differences in these measures among the study groups (see the Supplementary Appendix for further details).

Baseline demographic and clinical characteristics were similar across the study groups (Table 1). For the overall population, the mean (±SD) age was 42.5±13.7, women comprised 76% of patients, 85% were white, the mean body weight was 82.4±21.9 kg, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 29.8±7.3. The mean IgE level for patients at baseline was elevated:

168.2±231.9 IU per milliliter (normal range, 13 to 127), with a median of 78 IU per milliliter. The mean time since the diagnosis of chronic idiopathic urticaria was 6.5±8.6 years, the mean number of previous medications for chronic idiopathic urticaria was 4.3±2.7 (Table S1 in the Supplementary Appendix), the mean in-clinic UAS was 5.3±0.7, the mean UAS7 was 30.7±6.8, the weekly itch-severity score was 14.0±3.7, the weekly score for the number of hives was 16.7±4.3, and the use of rescue medication was 7.3±7.8 tablets per week. Angioedema was present during the week before randomization in 41% of patients.

The mean rates of diary compliance were high (>97%) and did not differ significantly across all study groups during the treatment period (Table S2 in the Supplementary Appendix).

EFFICACY

Baseline weekly itch-severity scores were approximately 14 in all treatment groups (Table 1). The mean changes from baseline in weekly itch-severity scores at week 12 (primary end point) were significantly improved in the group receiving 150 mg of omalizumab (–8.1±6.4, P=0.001) and 300 mg of omalizumab (–9.8±6.0, P<0.001) but not in the group receiving 75 mg of omalizumab (–5.9±6.5, P=0.46), as compared with placebo (–5.1±5.6) (Table 2). The reductions from baseline in mean weekly itch-severity scores were dose-responsive with all three omalizumab doses and were better than the placebo responses at the time points before week 12 (Fig. 2A). After week 12 (follow-up period), the mean weekly itch-severity scores for all omalizumab groups increased to reach values similar to those in the placebo group and did not return to baseline values for the duration of follow-up. Sensitivity analyses for the primary end point that used different methods for handling missing data showed similar results to those of the primary analysis (Tables S3, S4, and S5 in the Supplementary Appendix).

There was a significant difference between the group receiving either 150 mg or 300 mg of omalizumab and the placebo group with respect to all prespecified secondary end points (changes from baseline in UAS7 and the weekly score for the number of hives, the time to the MID in weekly itch-severity scores, the proportion of patients with a UAS7 of ≤6, the proportion of patients with the MID response in weekly itch-severity scores, the change from baseline in the score for the size of the largest hive, the change from baseline in the overall Dermatology Life Quality Index, and the proportion of angioedema-free days from weeks 4 to 12) (Table 2, and Table S6 and Fig. S1 through S6 in the Supplementary Appendix), except for the difference in the number of angioedema-free days from week 4 to week 12, which reached significance only in the 300-mg group. Similar to weekly itch-severity scores, the weekly score for the number of hives decreased with all three doses of omalizumab to a greater extent than with placebo throughout the 12-week treatment period, with the largest difference observed in the 300-mg group (Fig. 2B). After week 12 (i.e., during the follow-up period), the mean weekly score for the number of hives for all omalizumab groups increased to reach values similar to those in the placebo group and did not return to baseline values for the duration of follow-up.

The exploratory analysis of scores on the Chronic Urticaria Quality-of-Life Questionnaire showed similar results to those from the other end points that were assessed in this study (Fig. S7 in the Supplementary Appendix).

In the post hoc analyses at week 12, the proportions of patients who were completely free of hives were 10% in the placebo group, 18% in the group receiving 75 mg of omalizumab, 23% in the group receiving 150 mg of omalizumab, and 53% in the group receiving 300 mg of omalizumab; among patients who were free of both hives and itching (i.e., a UAS7 score of 0), the proportions were 5%, 16%, 22%, and 44%, respectively (Fig. S8 and S9 in the Supplementary Appendix).

At baseline, the mean number of diphenhydramine tablets (25 mg) that patients were taking as rescue medication was 7.3±7.8. The mean changes from baseline in the weekly number of tablets were –2.3±6.1 in the group receiving 75 mg of omalizumab (P=0.91), –3.7±6.0 in the group receiving 150 mg of omalizumab (P=0.07), and –4.1±5.4 in the group receiving 300 mg of omalizumab (P=0.01), as compared with –2.2±5.0 in the placebo group (Fig. S10 in the Supplementary Appendix).

In prespecified subgroup analyses for the primary end point, no meaningful interpretation of results or definitive conclusions could be made

because of the reduced sample sizes for these analyses (data not shown).

SAFETY

The percentages of patients with at least one adverse event were similar across the treatment groups: 61% in the placebo group, 59% in those receiving 75 mg of omalizumab, 67% in those receiving 150 mg of omalizumab, and 65% in those receiving 300 mg of omalizumab (Table 3, and Table S7 in the Supplementary Appendix). During the 28-week study period, there were reports of nine serious adverse events, with five reported in the group receiving 300 mg of omalizumab (6%), two in the placebo group (3%), and one each in the groups receiving 75 mg and 150 mg of omalizumab (1% for each). Most of the adverse events were reported in the 150-mg and 300-mg groups during the follow-up period, when no drug was being administered (Table 3, and Table S8 in the Supplementary Appendix). No deaths or episodes of anaphylactic shock were reported during the study. There were no major imbalances in any of the system organ classes affected by adverse events, with the exception of headache, with more cases being reported in the group receiving 150 mg of omalizumab than in the placebo group. (Additional details on safety information are provided in the Supplementary Appendix.)

DISCUSSION

In this study, we found that omalizumab administered as three doses of 150 mg or 300 mg at 4-week intervals significantly reduced symptoms, as compared with placebo, in patients with chronic idiopathic urticaria who remained symptomatic despite the use of approved doses of H_1-antihistamines. Significant and clinically meaningful effects were seen for patients receiving either 150 mg or 300 mg of omalizumab in the change from baseline in the weekly itch-severity score (primary end point) and all secondary end points at week 12, with the exception of the proportion of angioede-

Table 1. Baseline Characteristics of the Patients (Modified Intention-to-Treat Population).*

Characteristic	Placebo (N=79)	Omalizumab		
		75 mg (N=82)	150 mg (N=82)	300 mg (N=79)
Demographic				
Age — yr	43.1±12.5	39.7±15.0	43.0±13.2	44.3±13.7
Age group — no. (%)				
12–17 yr	2 (3)	4 (5)	2 (2)	2 (3)
18–40 yr	30 (38)	42 (51)	32 (39)	31 (39)
41–64 yr	44 (56)	31 (38)	45 (55)	39 (49)
≥65 yr	3 (4)	5 (6)	3 (4)	7 (9)
Female sex — no. (%)	55 (70)	61 (74)	65 (79)	63 (80)
Race — no. (%)†				
White	70 (89)	64 (78)	70 (85)	68 (86)
Nonwhite	6 (8)	16 (20)	6 (7)	9 (11)
Not available	3 (4)	2 (2)	6 (7)	2 (3)
Weight				
Mean — kg	84.3±25.7	82.8±21.2	82.4±20.7	80.3±19.9
<80 kg — no. (%)	41 (52)	43 (52)	41 (50)	41 (52)
Body-mass index‡	30.0±7.7	30.2±7.7	30.0±7.3	29.0±6.3
Clinical				
Time since diagnosis of chronic idiopathic urticaria — yr§				
Mean	7.2±10.7	5.3±7.1	7.2±8.9	6.1±7.3
Median	3.3	2.5	3.9	3.5

Table 1. (Continued.)

Characteristic	Placebo (N=79)	Omalizumab		
		75 mg (N=82)	150 mg (N=82)	300 mg (N=79)
Previous medications for chronic idiopathic urticaria — no.	4.4±2.9	4.1±2.1	4.5±3.2	4.3±2.5
In-clinic UAS¶	5.3±0.7	5.4±0.8	5.3±0.7	5.3±0.7
UAS7‖**	31.0±6.6	30.7±6.9	31.4±7.0	29.5±6.9
Weekly itch-severity score**††	14.0±3.4	14.0±3.7	14.2±4.1	13.7±3.5
Weekly score for no. of hives**‡‡	17.0±4.2	16.8±4.2	17.1±4.1	15.8±4.6
Overall score on Dermatology Life Quality Index§§	12.6±5.9¶¶	12.6±6.5	13.0±6.1	12.7±6.4
Presence of angioedema — no. (%)**	30 (38)	31 (38)	38 (46)	32 (41)
Weekly no. of diphenhydramine tablets (25 mg) as rescue medication**	7.1±7.7	7.8±9.0	7.5±7.7	6.7±6.8

* Plus–minus values are means ±SD. The modified intention-to-treat population included all patients who had undergone randomization and received at least one dose of a study drug. There were no significant differences among the groups at baseline. Percentages may not total 100 because of rounding.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Data are for 77 patients in the placebo group, 80 in the group assigned to receive 75 mg of omalizumab, 81 in the group assigned to receive 150 mg of omalizumab, and 76 in the group assigned to receive 300 mg of omalizumab.
¶ The urticaria activity score (UAS) ranges from 0 to 6, with higher scores indicating greater activity. This value was defined as the largest value among those obtained on screening visits on days 14 and 7 before randomization and on the day 1 visit.
‖ The UAS during a 7-day period (UAS7) ranges from 0 to 42, with higher scores indicating greater activity and a minimally important difference (MID) of 9.5 to 10.5.
** These values are based on data that were collected in a patient daily diary in the week before randomization.
†† Daily scores for itch severity were 0 indicating none, 1 indicating mild, 2 indicating moderate, and 3 indicating severe, with weekly totals ranging from 0 to 21 and an MID of 5 or more points.
‡‡ Daily scores for the number of hives were 0 indicating none, 1 indicating 1 to 6, 2 indicating 7 to 12, and 3 indicating ≥12, and an MID of 5.0 to 5.5 for the weekly average.
§§ The Dermatology Life Quality Index ranges from 0 to 30, with higher scores indicating a worse quality of life and an MID of 2.24 to 3.10.
¶¶ This value was measured in 78 patients in the placebo group.

ma-free days during week 4 through week 12 in the group receiving 150 mg of the drug. Furthermore, the safety profile for omalizumab was similar to that previously reported in omalizumab-treated patients with allergic asthma.[13,14,27,28] However, the majority of serious adverse events occurred in the group receiving the highest dose (300 mg) of omalizumab.

Omalizumab had an onset of effect within a week after initiation in this patient population (Fig. 2, and Fig. S1 in the Supplementary Appendix). The median time to MID response in the weekly itch-severity score was significantly shorter in the group receiving 300 mg of omalizumab (1 week) and in the group receiving 150 mg (2 weeks) than in the placebo group (4 weeks) (Table 2). The phase 2 studies also showed reductions in the UAS and UAS7 during the first week of omalizumab treatment.[20,21]

The duration of suppression in the weekly itch-severity score after week 12 was greater in patients receiving the higher doses (150 mg and 300 mg) of omalizumab. There did not appear to be a rebound increase in symptoms back to baseline during the course of the study once omalizumab had been discontinued. However, it is possible that some patients' symptoms during follow-up may have remained under better control because they were allowed to take an additional H_1-antihistamine during this period. In the placebo group, after an initial small reduction in the mean weekly itch-severity score during the first couple of weeks, scores remained unchanged for the remainder of the study period. The observation that symptoms gradually recur after discontinuation (as shown by the increase in mean itch-severity scores and scores for the number of hives after week 12) suggests that omalizumab

Table 2. Primary and Secondary Efficacy End Points (Modified Intention-to-Treat Population).*

End Point	Placebo (N=79)	Omalizumab		
		75 mg (N=82)	150 mg (N=82)	300 mg (N=79)
Primary end point				
Itch-severity score				
Change from baseline to wk 12				
Mean	−5.1±5.6	−5.9±6.5	−8.1±6.4	−9.8±6.0
Median (range)	−4.0 (−20.5 to 6.0)	−6.5 (−21.0 to 10.0)	−8.5 (−21.0 to 5.1)	−10.5 (−21.0 to 4.5)
Least-squares mean difference for treatment vs. placebo (95% CI)†	NA	−0.7 (−2.5 to 1.2)	−3.0 (−4.9 to −1.2)‡	−4.8 (−6.5 to −3.1)§
Secondary end points				
Weekly no. of hives				
Change from baseline to week 12				
Mean	−5.2±6.6	−7.2±7.0	−9.8±7.3	−12.0±7.6
Median (range)	−2.4 (−19.5 to 5.5)	−6.5 (−21.0 to 8.5)	−10.0 (−21.0 to 3.0)	−13.0 (−21.0 to 10.5)
Least-squares mean difference for treatment vs. placebo (95% CI)¶	NA	−2.0 (−4.1 to −0.1)	−4.5 (−6.7 to −2.4)§	−7.1 (−9.3 to −4.9)§
Patients with UAS7 ≤6 at wk 12 — no. (%)	15 (19)	22 (27)	35 (43)‡	52 (66)§
Overall score on Dermatology Life Quality Index‖				
Change from baseline to week 12				
Mean	−6.1±7.5	−7.5±7.2	−8.3±6.3	−10.2±6.8
Median (range)	−5.0 (−25.0 to 13.0)	−7.0 (−26.0 to 11.0)	−8.0 (−27.0 to 6.0)	−10.0 (−27.0 to 8.0)
Least-squares mean difference for treatment vs. placebo (95% CI)**	NA	−1.7 (−3.8 to 0.5)	−2.5 (−4.6 to −0.4)††	−3.8 (−5.9 to −1.7)§
Angioedema-free days from wk 4 through wk 12 — %‡‡				
Mean	89.2±19.0	93.5±14.9	91.6±17.4	95.5±14.5
Median (range)	100.0 (15.4 to 100.0)	100.0 (30.4 to 100)	100.0 (14.3 to 100.0)	100 (17.9 to 100.0)§

* Plus–minus values are means ±SD. Missing scores for week 12 were imputed from baseline weekly scores. NA denotes not applicable.
† Least-squares means were estimated with the use of an analysis of covariance (ANCOVA) model stratified according to the baseline weekly itch-severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg).
‡ P<0.01 for the comparison with placebo.
§ P<0.001 for the comparison with placebo.
¶ The ANCOVA model was stratified according to the baseline weekly number of hives (<median vs. ≥median) and baseline weight (<80 kg vs. ≥80 kg).
‖ The baseline score on the Dermatology Life Quality Index was obtained before administration of a study drug on day 1, and there was no imputation for missing scores for week 12.
** The ANCOVA model was stratified according to the baseline overall score on the Dermatology Life Quality Index (<median vs. ≥median) and baseline weight (<80 kg vs. ≥80 kg).
†† P=0.02 for the comparison with placebo.
‡‡ Angioedema-free days were defined as the number of days for which the patient responded "no" to the angioedema question in the daily diary divided by the total number of days with a nonmissing diary entry starting at the week 4 visit and ending the day before the week 12 visit. Patients who withdrew before the week 4 visit or who had missing responses for more than 40% of the daily diary entries between the week 4 and week 12 study visits were not included in this analysis.

Figure 2 (facing page). Mean Weekly Symptom Scores.
Mean weekly symptom scores are shown for itch severity, with totals ranging from 0 to 21 and with higher scores indicating greater severity (Panel A), and the number of hives, with daily totals of 0 indicating none, 1 indicating 1 to 6 hives, 2 indicating 7 to 12 hives, and 3 indicating more than 12 hives (for weekly totals of 0 to 21) (Panel B). Data are for patients in the modified intention-to-treat population (i.e., all patients who underwent randomization and received at least one dose of a study drug).

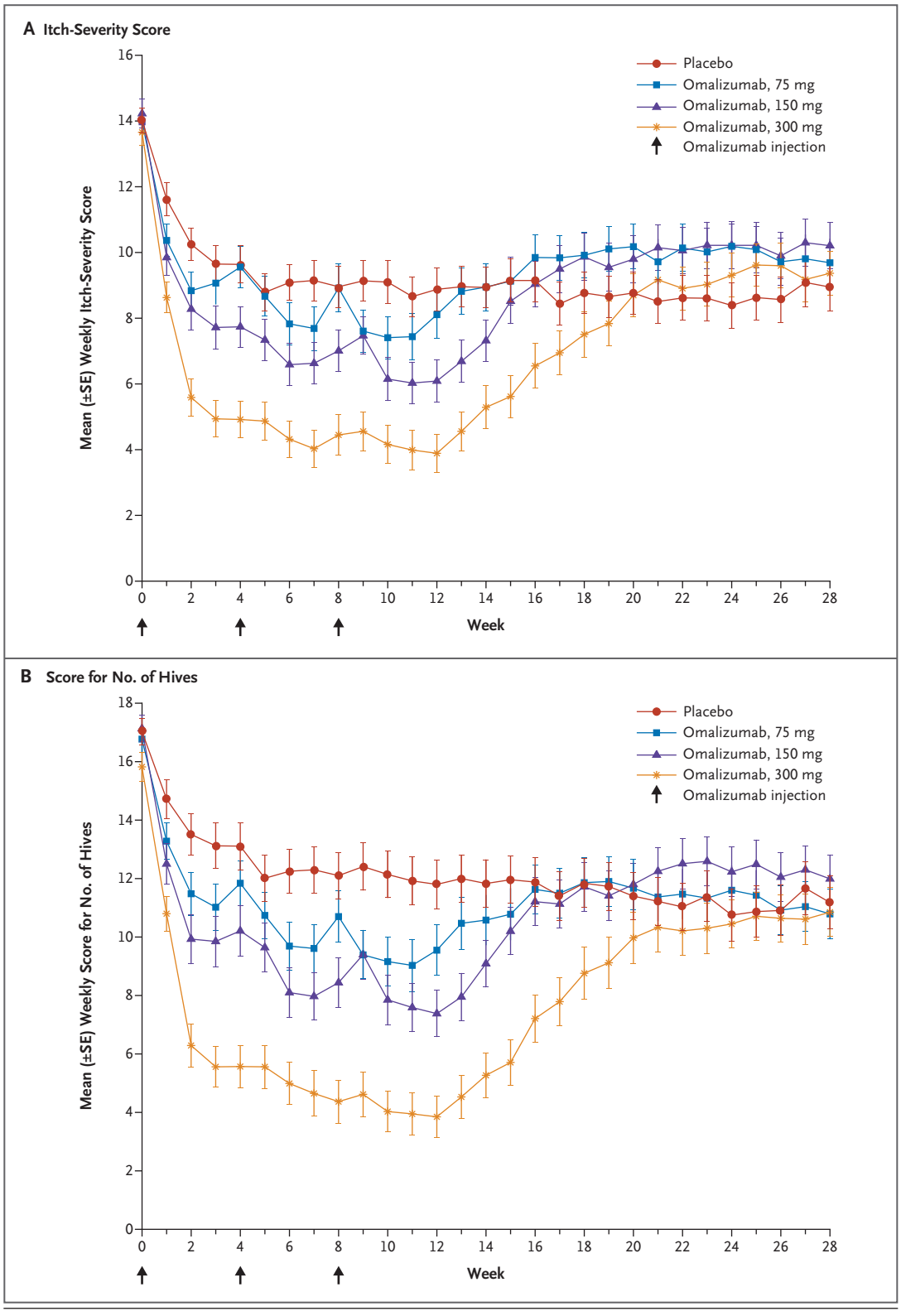

Table 3. Adverse Events (Safety Population).*

Event	Placebo (N=79)	Omalizumab		
		75 mg (N=76)	150 mg (N=88)	300 mg (N=79)
		no. of patients (%)		
At least one adverse event	48 (61)	45 (59)	59 (67)	51 (65)
Any adverse event leading to discontinuation of study drug	0	3 (4)	2 (2)	0
Early withdrawal from study due to an adverse event	1 (1)	0	1 (1)	0
Any serious adverse event†	2 (3)	1 (1)	1 (1)	5 (6)
Death	0	0	0	0
Any adverse event suspected to be caused by study drug	3 (4)	7 (9)	8 (9)	7 (9)
Any severe adverse event‡	7 (9)	4 (5)	5 (6)	6 (8)

* The safety population was defined according to the treatment actually received. A complete list of adverse events is provided in Table S7 in the Supplementary Appendix.

† The nine reported serious adverse events were pneumonia and hemorrhoids in one patient each in the placebo group; angioedema in one patient in the 75-mg group; angioedema and idiopathic urticaria in one patient in the 150-mg group; and melanoma in situ, nephrolithiasis, idiopathic urticaria, tonsillectomy, and melena in one patient each in the 300-mg group. After a review of the hospital discharge summary after the database lock, it was determined that the patient with melena had no anemia; the cause of hospital admission was elective endoscopy for nonanemic melena. The patient underwent upper gastrointestinal endoscopy and colonoscopy, which revealed only diverticulosis with no other potential source of bleeding. Thus, it was determined that this patient had a nonserious event of nonanemic melena rather than a serious adverse event, as initially reported. Additional details about the serious adverse events are provided in Table S8 in the Supplementary Appendix.

‡ A severe adverse event was defined as the occurrence of symptoms causing an inability to perform usual social and functional activities. A complete description of the severe adverse events is provided in the Safety section in the Supplementary Appendix.

administered as three doses at 4-week intervals did not substantially modify the basic underlying disease process in this population during this time period (Fig. 2).

The mechanism by which omalizumab works to improve urticaria has not been fully elucidated. It has been reported that patients with active chronic idiopathic urticaria have abnormal basophil function, including suppression of the high-affinity IgE receptor (FcεRI) pathway (related to altered expression of Src homology 2–containing inositol phosphatase), blood basopenia, and recruitment of basophils to skin-lesion sites.[12] In patients with chronic idiopathic urticaria in remission, blood basopenia and suppressed FcεRI function revert toward normal.[12] In previous studies, the binding of circulating IgE by omalizumab has been shown to lead to a reduction in free IgE within hours after administration and down-regulation of FcεRI on blood basophils within 2 weeks; in mast cells, reduction in FcεRI expression and degranulation typically occurs after 8 weeks.[15,29,30] This study was not designed to further elucidate the mechanism of action of omalizumab in patients with chronic idiopathic urticaria.

In conclusion, during the initial 12 weeks of our study, omalizumab at doses of 150 mg and 300 mg significantly improved outcomes as reported by patients with chronic idiopathic urticaria who remained symptomatic despite the use of approved doses of H_1-antihistamines. The number of patients who were treated was too small to draw any definitive safety conclusions, but serious adverse events were more common in the group treated with the highest dose of omalizumab. Further work is needed before the exact role of omalizumab in the treatment of chronic idiopathic or spontaneous urticaria can be defined.

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