

Once-daily fexofenadine treatment for chronic idiopathic urticaria: a multicenter, randomized, double-blind, placebo-controlled study

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Background: Chronic idiopathic urticaria (CIU) can have a profound effect on patients' health and quality of life.

Objective: To evaluate the efficacy and safety of once-daily dosing of fexofenadine hydrochloride, 180 mg, on CIU.

Methods: This randomized, double-blind, parallel-group, placebo-controlled study consisted of a placebo run-in period followed by a 4-week treatment period. Patients 12 years and older with active CIU were randomized 2:1 to receive once-daily fexofenadine, 180 mg, or placebo. The primary end points were change from baseline in mean daily number of wheals (MNW score) and mean daily severity of pruritus during treatment. Secondary efficacy measures included modified total symptom scores and MNW and pruritus severity scores evaluated weekly and instantaneously at trough drug levels.

Results: Patients administered fexofenadine ($n = 163$) experienced significantly greater improvements in MNW and pruritus severity scores compared with the placebo group ($n = 92$) ($P < .001$ for both). Similarly, throughout treatment and at each individual week, the mean reductions in modified total symptom scores were significantly greater in the fexofenadine group ($P \leq .005$ for all comparisons vs placebo). The mean reductions in instantaneous MNW and pruritus severity scores were greater in patients in the fexofenadine group than in those who received placebo (MNW score: $P = .015$; pruritus severity score: $P < .001$). There were no significant differences in the frequency of treatment-emergent adverse events between the 2 treatment groups.

Conclusion: A once-daily dose of fexofenadine hydrochloride, 180 mg, offered effective, well-tolerated relief for the management of CIU.

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INTRODUCTION

Chronic idiopathic urticaria (CIU) is a distressing condition for many individuals. In keeping with the elusive nature of CIU, the prevalence of the disease has not been unequivocally established,¹ but estimates suggest that 15% to 20% of the population experiences at least 1 episode of urticaria in their lifetime^{2,3}; of these, 5% to 10% are diagnosed as having CIU.⁴

Chronic idiopathic urticaria is characterized by episodes of short-lived, recurrent, pruritic wheals that are circumscribed, raised, and erythematous.⁵ Approximately 50% of patients with CIU also experience concurrent angioedema, which can cause burning and painful sensations.⁵ The duration of the disease varies among individuals; although the mean duration of CIU is 3 to 5 years, a small proportion of patients can have CIU for more than 20 years.⁵ Despite the common presentation of symptoms, there are at least 2 subgroups of patients with CIU. The first subgroup consists of individuals with autoimmune chronic urticaria associated with autoantibodies

against either the high-affinity IgE receptor FcεR1^{6,7} or, less commonly, IgE itself.⁸ It is estimated that 40% to 50% of patients previously designated as having CIU actually have this autoimmune urticaria.⁹ The other group of patients with CIU are truly "idiopathic" because there is no known cause for the disease.⁶

However, irrespective of the cause of the CIU, the effect of this highly visible condition extends beyond the physical signs and symptoms that characterize it: the disease can have a profound impact on quality of life (QoL). Using a disease-specific, purpose-designed questionnaire and the Nottingham Health Profile, O'Donnell et al¹⁰ demonstrated that patients with chronic urticaria had considerable disability, handicap, and reduced QoL. This reduced QoL was linked to patient distress in areas of mobility, sleep, and energy; they also experienced pain, social isolation, and altered emotional reactions.¹⁰ To put this level of QoL impairment into context, patients in this survey experienced the same degree of impairment as patients with coronary artery disease.¹⁰ Therefore, the ideal treatment for CIU would not only relieve the patient of the discomfort of the disease but would also improve QoL.

Although recognition of the autoimmune basis of CIU has opened up new avenues of therapy, such as the use of immunosuppressive drugs, the mainstay of treatment remains the scheduled use of H₁-receptor blockers or concomitant therapy with H₁- and H₂-receptor blockers.¹¹ Because older-

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generation H₁-receptor antagonists are associated with sedative and anticholinergic effects, second-generation H₁-antihistamines, which are more specific for the H₁-receptor, are preferred.^{12,13}

Fexofenadine is a nonsedating, long-acting, specific peripheral histamine H₁-receptor antagonist that has been shown to be effective and safe for the symptomatic relief of CIU.¹⁴ This assertion is supported by several double-blind, randomized clinical studies^{15–20} conducted in adults and children older than 12 years.

Data suggest that the optimal dose of fexofenadine is 60 mg twice daily.^{15–19} Indeed, this is the currently recommended dose in the United States for uncomplicated skin manifestations of CIU; for children aged 6 to 11 years, the recommended dose is 30 mg twice daily. The most beneficial once-daily dose of fexofenadine hydrochloride seems to be 180 mg,¹⁵ and this is the once-daily dosing regimen approved for CIU in Europe. The clinical efficacy of this dose has yet to be examined in a large clinical trial conducted in the United States. We report herein an investigation of the efficacy and safety of fexofenadine hydrochloride, 180 mg once daily, in the treatment of CIU as part of a large, US, multicenter, double-blind, randomized, placebo-controlled trial.

METHODS

Patients

Males and females 12 years and older with a diagnosis of CIU and a history of urticarial wheals at least 3 days per week for the 6 consecutive weeks before the first visit were eligible to participate in the study. Only nonpregnant females who were using reliable systemic medical or barrier contraception, who were surgically sterile, or who were postmenopausal were included. All patients were required to provide written informed consent to participate in the study. To qualify at baseline, an urticarial evaluation was performed at the first visit. Patients were required to have 1 or more wheals and to rate their pruritus reflectively during the previous 12 hours as at least 2 on a scale from 0 to 4 (0 = none and 4 = very severe). Symptom severity was also required to be evaluated by the investigator.

Patients were excluded if they were pregnant, were lactating, or had any of the following conditions: mental illness, malnutrition, blood dyscrasia, renal or hepatic insufficiency, chronic infection, drug abuse, alcoholism, malignancy, or malabsorption. Patients with a history of hypersensitivity to fexofenadine or drugs with a similar chemical structure or a history of unresponsiveness to antihistamine treatment were also ineligible. Patients were also excluded if they were treated with any investigational product in the 30 days before providing informed consent, required treatment during the study with drugs that were not permitted by the clinical study protocol, or were known to have serious cardiovascular, hepatic, endocrine, or other major systemic disease.

Study Design

This multicenter, randomized, double-blind, parallel-group, placebo-controlled study consisted of 6 or 7 visits and included a single-blind placebo run-in period for 2 to 5 days followed by a mean $\pm$ SD 28 $\pm$ 4-day treatment period. This study also examined QoL and pharmacokinetic variables, which will be reported elsewhere. The study complied with International Conference on Harmonisation, Good Clinical Practice guidelines, and the protocol was approved by an overarching review board (Schulman Associates Institutional Review Board Inc, Cincinnati, OH) and by local institutional review boards when required.

Placebo Run-in Phase

Patients who presented at visit 1 with a diagnosis of CIU and who were eligible for inclusion were given single-blind placebo and were instructed to take 1 tablet daily at 7 AM ($\pm$ 1 hour) for 2 to 5 days. Patients were issued diaries to be completed twice daily, once in the morning before dosing and then 12 hours later in the evening. Patients who were ineligible for inclusion at visit 1 were given a second opportunity to qualify for study entry at visit 1A (24 hours to 14 days after visit 1). Patients who qualified at visit 1A were also given single-blind placebo and diaries for the 2- to 5-day baseline period. Twice-daily diary assessments between visit 1 or 1A and visit 2 established the mean baseline urticarial scores.

Treatment Phase

At visit 2, patients were evaluated for continued eligibility in the study. To qualify for randomization, patients were required to meet all the screening inclusion criteria. In addition, an urticarial evaluation was performed by the investigator, and vital signs and any concomitant medication use and adverse events were recorded. Qualifying patients were given new diaries and were randomized in a 2:1 manner to receive either fexofenadine hydrochloride, 180 mg, or placebo once daily. Patients received double-blind study medication packaged in bottles that contained 40 tablets (enough medication for 40 days) and were instructed to take the first dose of medication at 7 AM ($\pm$ 1 hour) on the morning after visit 2 and each morning of the double-blind treatment phase.

Patients returned to the clinic for visits 3, 4, 5, and 6, corresponding to 1, 2, 3, and 4 weeks, respectively, after the initiation of double-blind treatment. At each visit, diaries were collected and reviewed, and patients were evaluated for compliance, concomitant medication use, and adverse events. Physicians performed a CIU evaluation using the same scales as the patient. New diaries were given at each visit, and patients were instructed to return in 1 week for the next visit, except at the final visit (visit 6). Patients and investigators evaluated the global efficacy of treatment of urticaria at visit 6.

Efficacy Assessments and Safety Measures

The primary efficacy assessments were the change from baseline in patients' mean daily number of wheals (MNW score) and mean daily severity of pruritus score during the

28-day double-blind treatment period. Pruritus severity was rated on a scale from 0 to 4 in which 0 indicates none; 1, mild, not annoying or troublesome; 2, moderate, annoying and troublesome, may interfere with normal daily activity and sleep; 3, severe, very annoying and troublesome, substantially interfering with sleep and daily activities; and 4, very severe, warrants a visit to the physician. These variables were recorded in the patients' daily diaries the morning before dosing and 12 hours later as reflective evaluations of symptom severity during the previous 12 hours.

Secondary efficacy assessments included individual assessments of the number, frequency, size, and duration of lesions and the severity of pruritus. Each of these assessments were evaluated as follows, and the scores for each element were summed to obtain a modified total symptom score (MoTSS): number of wheals evaluated on a scale from 0 to 3 (0 = none; 1 = 1–10 wheals; 2 = 11–20 wheals; and 3 = >20 wheals); number of separate wheal episodes (>1 hour apart) evaluated on a scale from 0 to 3, with a score of 3 meaning 3 or more episodes; average size of lesions, measured on a scale from 0 to 3, with a score of 3 meaning 3 inches or more; duration of lesions rated on a scale from 0 to 4 (0 = none; 1 = >4 hours; 2 = 4–12 hours; 3 = 12–24 hours; and 4 = 24 hours); and pruritus severity evaluated as described for the primary end point using the 5-point scale in which 0 corresponds to "none" and 4 corresponds to "severe." The MoTSS was calculated for the morning (AM 12-hour reflective score) and evening (PM 12-hour reflective score); from these 2 scores a daily mean score was also calculated.

Other secondary measures included patient and investigator independent global evaluations of the overall efficacy of treatment at the final or early-termination visit. The global efficacy evaluation consisted of a 5-point scale (0 = no improvement or worsening of symptoms; 1 = slight but insufficient improvement; 2 = definite improvement; 3 = substantial improvement; and 4 = complete disappearance of symptoms). In addition, the change from baseline in patients' MNW scores and mean daily pruritus severity scores during the 28-day treatment period were evaluated instantaneously before each dose to measure clinical efficacy at trough.

Safety was evaluated by adverse event reporting throughout the study; 12-lead electrocardiography; clinical laboratory tests, including hematologic analysis, urine analysis, and clinical chemistry measurements; and physical examinations. All of these assessments were performed at visit 1 or 1A and at the final visit (visit 6).

Statistical Procedures

The study was powered to test 2 end points: the difference in change from baseline in the number of wheals between the fexofenadine and placebo groups and the difference in change from baseline in pruritus severity scores between groups. We required 128 and 64 patients to be randomized to receive fexofenadine and placebo, respectively (2:1 randomization). This sample size was calculated to provide at least 90%

power to detect differences in both end points at a .05 significance level, assuming an underlying difference of 0.56 U and a common SD of 1.03 U. The efficacy study population evaluated was the intention-to-treat population (ITT), defined as patients who took the study medication and had baseline and at least 1 postbaseline measure. The safety analysis was performed on all randomized patients who received at least 1 dose of study medication.

The primary efficacy variables were analyzed using an analysis of covariance model, which included terms for investigative site, treatment, and baseline evaluation (covariate adjustment). Missing evaluation primary efficacy data were imputed using the last observation carried forward method, and treatment comparisons were performed using the imputed data. Treatment by site and treatment by baseline interactions were evaluated and included in the final model if they were significant at an α level of .1. An α level of .05 (2-sided) was adopted for statistical significance for the primary end points. Major secondary efficacy end points were evaluated using a model similar to that used for the primary end point.

RESULTS

Of 483 patients who were screened, 358 were enrolled into the single-blind placebo run-in phase of the study. Of these 358 patients, 259 from 40 sites were randomized to receive either placebo ($n = 92$) or fexofenadine hydrochloride, 180 mg ($n = 167$), once daily. The ITT population was composed of 255 patients (163 in the fexofenadine group and 92 in the placebo group). There were no statistically significant differences between the placebo and fexofenadine groups at baseline in any of the demographic variables or in the primary and major secondary urticarial assessments in the ITT population (Table 1).

Primary Efficacy Evaluation

Improvement in wheal score. During the 28-day treatment period, patients treated with fexofenadine experienced a significant decrease in the mean daily number of wheals (MNW score) compared with patients who received placebo ($P < .001$) (Fig 1).

Improvement in pruritus. Similarly, the improvement during the 28-day treatment period in the pruritus severity score observed in the fexofenadine group was significantly greater than that observed in the placebo group ($P < .001$) (Fig 2).

Secondary Efficacy Assessments

Improvements in wheals and pruritus. Weekly analysis of the MNW score and the mean pruritus severity score showed that patients treated with fexofenadine experienced a significantly greater reduction in the MNW score compared with patients randomized to receive placebo for each week of the 4-week treatment period ($P = .003$ to $P < .001$). In addition, treatment with fexofenadine significantly improved the pruritus severity score at all weekly assessments ($P = .002$ to $P < .001$).

Statistically significant improvements in favor of fexofenadine were also observed when total number of wheals and

Table 1. Baseline Demographics and Symptom Scores for the Intention-to-Treat Population

	Placebo group (n = 92)	Fexofenadine group (n = 163)
Sex, No.		
M	25	41
F	67	122
Age, No.		
<65 y	89	158
≥65 y	3	5
Racial category, No. (%)		
White	66 (71.7)	118 (72.4)
Black	8 (8.7)	20 (12.3)
Asian/Oriental	4 (4.3)	5 (3.1)
Other	14 (15.2)	20 (12.3)
Pruritus severity score, mean (SD)*	2.2 (0.55)	2.3 (0.58)
Number of wheals score, mean (SD)†	1.9 (0.67)	1.9 (0.74)

*Pruritus severity score: 0 = none; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe.

†Number of wheals score: 0 = 0 wheals; 1 = 1–10 wheals; 2 = 11–20 wheals; and 3 = >20 wheals.

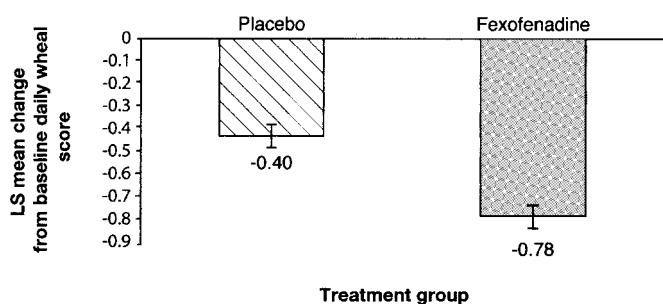


Figure 1. Overall mean change from baseline in daily mean number of wheals score (0 = 0 wheals; 1 = 1–10 wheals; 2 = 11–20 wheals; and 3 = > 20 wheals) in the placebo (n = 92) and fexofenadine (n = 163) groups ($P < .001$). Error bars represent SE. LS, least squares.

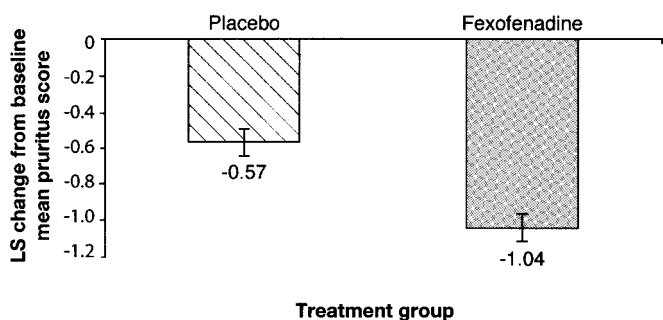


Figure 2. Overall mean change from baseline in mean pruritus severity score (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) in the placebo (n = 92) and fexofenadine (n = 163) groups ($P < .001$). Error bars represent SE. LS, least squares.

pruritus severity were analyzed separately in the morning and evening. Overall ($P < .001$) and at each weekly evaluation, the morning and evening number of wheals were significantly lower in the fexofenadine group compared with the placebo group ($P \leq .03$ and $P \leq .001$, respectively) (Fig 3A). Sim-

ilarly, pruritus was less severe during the treatment period ($P < .001$) and at each weekly evaluation for the morning and evening scores ($P \leq .02$ and $P \leq .001$, respectively) (Fig 3B).

Wheals and pruritus at trough drug levels. The MNW and pruritus severity scores were evaluated immediately before dosing in the morning to evaluate the efficacy of treatment at trough drug levels. During the 28-day study, the mean reductions in instantaneous MNW and pruritus severity scores for the fexofenadine-treated patients were significantly greater than those of the placebo-treated patients ($P < .02$ and $P < .001$, respectively). In addition, at each weekly evaluation, patients in the fexofenadine group experienced a significantly greater reduction from baseline in instantaneous MNW scores at weeks 1 and 2 and in instantaneous pruritus scores at weeks 1, 2, and 4 compared with the placebo group. At other weekly assessments there was a numerical trend in favor of fexofenadine, although this did not reach statistical significance at all weekly assessments.

Modified TSS. Between-treatment comparisons were made for the change in morning and evening reflective and mean daily MoTSSs (defined as the sum of the MNW, frequency of lesion, size of lesion, duration of lesion, and pruritus severity scores evaluated by patients). During the 28-day treatment and at all weekly assessments, mean reductions in morning reflective MoTSSs were significantly greater for patients in the fexofenadine group compared with those in the placebo group ($P < .001$ for the overall treatment period; $P = .005$ to $P < .001$ at each weekly evaluation). In addition, evaluation of the evening reflective MoTSSs showed significant improvements in favor of fexofenadine ($P < .001$ for the overall treatment period; $P < .001$ at each weekly evaluation). Analysis of the change in daily mean reflective MoTSSs demonstrated findings consistent with the morning and evening reflective analysis, whereby the mean decrease in mean MoTSS was significant for fexofenadine at all assessments, ie, throughout the 4-week study and at each individual week ($P < .001$ for all). Similar findings were observed with

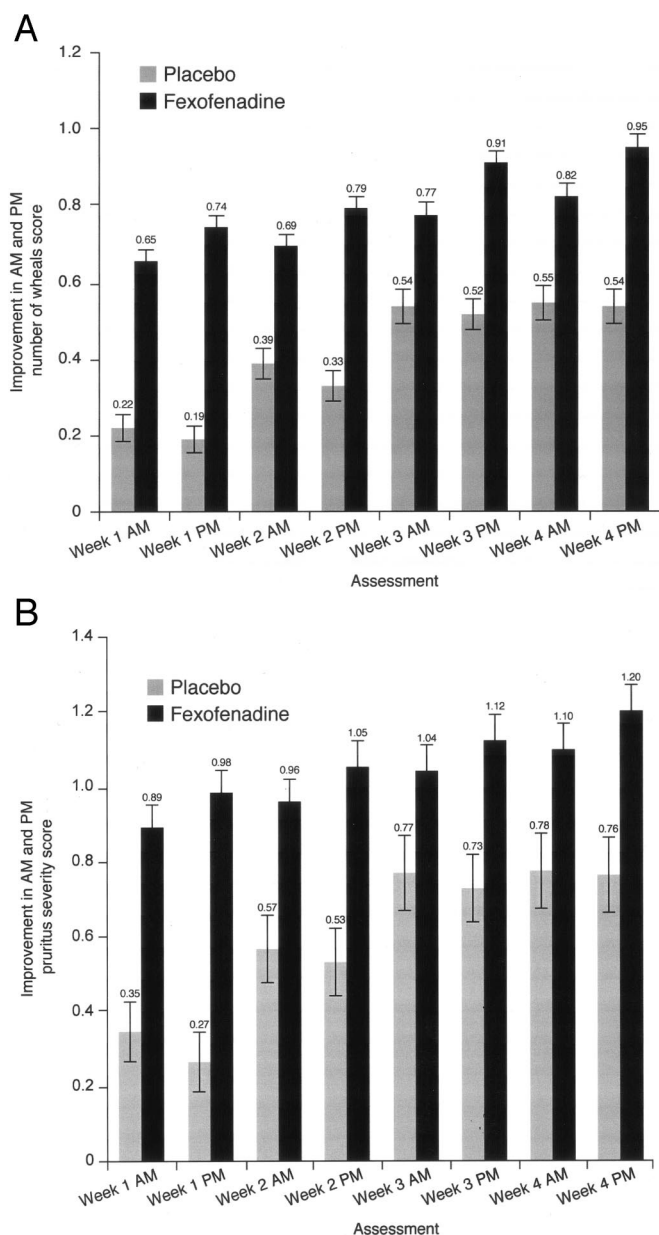


Figure 3. A, Improvements from baseline in reflective morning (AM) and evening (PM) mean number of wheals scores (0 = 0 wheals; 1 = 1–10 wheals; 2 = 11–20 wheals; 3 = >20 wheals). All between-treatment comparisons are significant ($P \leq .02$). B, Improvements from baseline in reflective morning and evening pruritus severity scores (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe). All between-treatment comparisons are significant ($P \leq .02$). Error bars represent SE.

evaluation of patients' and investigators' assessments of urticarial symptoms (data not shown).

Global evaluations of CIU. Patients and investigators provided global evaluations of each patient's urticarial status at week 4 (Table 2). Patients randomized to receive fexofena-

dine scored significantly higher in the global evaluations (according to patient and investigator assessments) than those in the placebo group ($P < .001$ for both). Using these global evaluation scores, patients were categorized as either "non-responders" (scoring 0 or 1) or "responders" (scoring ≥ 2). Number-needed-to-treat calculations ($1/[(\text{responder rate of fexofenadine treatment}) - (\text{responder rate of placebo})]$) reveal that 2.75 (patient evaluation) and 3.28 (investigator evaluation) patients need to be treated with fexofenadine for 1 patient to respond.

Dropout analysis. A smaller proportion of patients in the fexofenadine group (7%) dropped out of the study compared with patients in the placebo group (14%). The most common reason for withdrawing from the study was "lack of efficacy," which was reported by 46% (6/13) of those who dropped out of the placebo group and 8% (1/12) of the patients who dropped out of the fexofenadine group. Fexofenadine-treated patients withdrew from the study after a mean of 16.1 days compared with placebo-treated patients, who dropped out after a mean of 13.1 days. A Kaplan-Meier survival curve of the time to drop out revealed that patients randomized to receive fexofenadine remained in the study longer ($P = .046$, log-rank test of curve) (Fig 4).

Safety assessments. The safety-evaluable population consisted of 259 patients (167 in the fexofenadine group and 92 in the placebo group). There were no significant differences in the frequency of treatment-emergent adverse events (TEAEs) reported between the placebo (37%) and fexofenadine (31%) groups. The most commonly reported TEAE was headache: 5% in the fexofenadine group and 3% in the placebo group. In addition, headache was the most common event considered to be possibly related to study medication (2% and 0% in the fexofenadine and placebo groups, respectively). All TEAEs that were evaluated as possibly being related to the study medication were rated as mild or moderate in intensity. One serious TEAE was reported in the fexofenadine group. In this case, the patient experienced asthma that required hospitalization; however, the asthma was not considered to be related to the study drug. No clinically relevant changes from baseline to the end of treatment were observed in either group with respect to clinical laboratory data, vital signs, or electrocardiograms.

DISCUSSION

The results of this large, randomized, placebo-controlled, double-blind study demonstrate the efficacy and safety of once-daily dosing of fexofenadine hydrochloride, 180 mg, for the treatment of CIU. Compared with placebo, fexofenadine hydrochloride, 180 mg, resulted in significant reductions in the number of wheals and the severity of pruritus during the 28-day study and at weeks 1 to 4 inclusive. In addition, a once-daily dose of fexofenadine significantly reduced the MoTSS (sum of the MNW, frequency of lesion, size of lesion, duration of lesion, and pruritus severity scores) compared with placebo at all measured assessments. Furthermore, these improvements in individual symptom scores were rel-

Table 2. Investigator and Patient Global Evaluations of CIU at Week 4 in the Intention-to-Treat Population*

	Score†				
	0	1	2	3	4
Investigator global evaluation of CIU					
Placebo group (n = 91)	33 (36.3)	24 (26.4)	13 (14.3)	13 (14.3)	8 (8.8)
Fexofenadine group (n = 162)	21 (13.0)	31 (19.1)	35 (21.6)	54 (33.3)	21 (13.0)
Patient global evaluation of CIU					
Placebo group (n = 91)	31 (34.1)	29 (31.9)	14 (15.4)	11 (12.1)	6 (6.6)
Fexofenadine group (n = 162)	21 (13.0)	27 (16.7)	38 (23.5)	57 (35.2)	19 (11.7)

Abbreviation: CIU, chronic idiopathic urticaria.

*Data are given as number (percentage) of patients.

†0 = no improvement or worsening of symptoms; 1 = slight but insufficient improvement; 2 = definite improvement; 3 = substantial improvement; and 4 = complete disappearance of symptoms. Patients were categorized as either “nonresponders” (scoring 0 or 1) or “responders” (scoring ≥ 2).

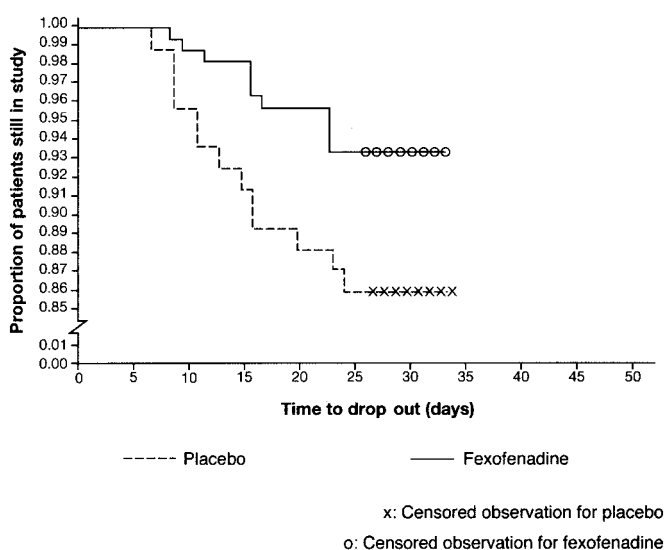


Figure 4. Kaplan-Meier plot of time to drop out in the intention-to-treat population ($P = .046$, log-rank test).

evant to the study population because patients in the fexofenadine group scored higher in the global evaluations of CIU status, evaluated by patients and investigators, than those in the placebo group. Indeed, according to patient evaluations, if those who scored 2 or more in the global evaluations of CIU status are regarded as responders, then only 2.75 patients require treatment with fexofenadine for 1 patient to experience at least a “definite improvement” in symptoms. Patients who received fexofenadine also continued treatment longer than those who received placebo. These efficacy results were achieved while maintaining a favorable safety profile.

Despite emerging new evidence of the autoimmune basis of the disease, antihistamines remain the mainstay of therapy for the treatment of CIU.²¹ Although immunosuppressive drugs such as methotrexate, tacrolimus, cyclosporine, intravenous immunoglobulins, and plasmapheresis have been used to treat patients refractory to conventional antihistamine treatment, these therapies can be highly invasive and are

associated with serious adverse effects.^{22,23} Therefore, the selection of an appropriate antihistamine is an important initial step in the successful management of CIU. These results also illustrate that efficacy and safety are maintained with once-daily dosing, which may offer greater convenience to patients and enhance compliance. The finding that instantaneous MNW and pruritus severity scores were significantly improved at trough drug levels with once-daily dosing over placebo during the 28-day study implies that fexofenadine is suitable for CIU at this dose level.

The results of the present study support those of a large, multicenter, double-blind, parallel-group, placebo-controlled, dose-ranging study¹⁵ in which 222 adults were randomized to receive either fexofenadine hydrochloride (60, 120, 180, or 240 mg) or placebo daily for 6 weeks. The combined fexofenadine groups showed a significant dose-dependent reduction in mean TSS, defined as the sum of pruritus severity scores and the number of wheals, compared with placebo ($P = .002$).¹⁵ Furthermore, the study suggested that 180 mg once daily is the optimal dose for the treatment of CIU because this dose significantly reduced the number of wheals compared with placebo ($P = .006$).¹⁵ These data are supported by a recent double-blind, placebo-controlled study²⁰ of fexofenadine hydrochloride, 180 mg once daily, conducted in Germany.

The safety and efficacy of twice-daily doses of fexofenadine hydrochloride (20, 60, 120, and 240 mg twice daily) during a 4-week period has been established in 2 double-blind, randomized, placebo-controlled studies.^{16,17} In both trials, all doses of fexofenadine were effective in relieving pruritus and in decreasing the number of wheals. Fexofenadine-treated patients also reported less interference with sleep and daily activities compared with those randomized to receive placebo.^{16,17} Furthermore, studies^{18,19} in Japanese and Thai patients have confirmed that the effectiveness of fexofenadine hydrochloride (60 mg twice daily) is not limited by ethnicity or by any genotypic variation between the different populations studied.

Many double-blind, randomized clinical studies have evaluated the efficacy of newer-generation antihistamines available for the treatment of CIU. Fexofenadine,^{15–17,20} lorata-

dine,^{24,25} cetirizine,^{26,27} and desloratadine^{28,29} have been shown to be safe and effective therapies for the disease. However, newer-generation antihistamines, like their predecessors, can be differentiated in terms of their selectivity for the H₁-receptor and their ability to cross the blood-brain barrier. One way such differences become manifest is in the varying potential of the newer-generation antihistamines to cause sedation, especially at higher-than-recommended doses.³⁰ Indeed, cetirizine is considered mildly sedating at recommended doses, and loratadine^{31–33} and desloratadine^{34,35} cause psychomotor impairment at high doses.

The potential impairment at higher doses is particularly pertinent to the treatment of urticaria for 3 distinct reasons. First, patients with CIU are occasionally prescribed much higher doses than is recommended to achieve symptom control.³⁶ Second, overuse of antihistamines is not uncommon, particularly when relief is not immediately forthcoming.³⁷ Finally, CIU is associated with considerable suffering in terms of diminished QoL and work productivity, so any agent used to relieve symptoms should not exacerbate any existing impairment. Of the newer-generation antihistamines available for the treatment of CIU, fexofenadine is the only nonsedating agent, even up to 3 times the recommended daily dose.³⁶

This study demonstrates that fexofenadine hydrochloride, 180 mg once daily, offers effective and safe relief of CIU by reducing pruritus severity; number, size, and duration of wheals; and number of wheal episodes. Therefore, fexofenadine represents an effective and safe treatment option with the convenience of once-daily dosing.

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