

A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria

Albert F. Finn, Jr, MD,^a Allen P. Kaplan, MD,^a Richard Fretwell, RN, BSN,^b Roger Qu, PhD,^b and Joseph Long, MS^b Charleston, SC, and Kansas City, Mo

Background: Symptoms of chronic idiopathic urticaria (CIU) include relentless itching and painful wheals, which can be physically and psychologically debilitating. Half of all patients with urticaria have angioedema, which is often disfiguring.

Objective: To evaluate the safety and efficacy of fexofenadine HCl for the treatment of CIU symptoms.

Methods: In this 4-week, multicenter, placebo-controlled study, 439 patients with moderate to severe pruritus and urticaria received 1 of 4 oral doses of fexofenadine HCl (20, 60, 120, or 240 mg twice a day) or placebo. Patients reflectively assessed (over the previous 12 hours) the severity of pruritus, the number of wheals, and the interference with sleep (7 AM) and normal activities (7 PM) due to urticaria. Efficacy measures included a change from baseline of daily mean pruritus score (MPS), daily mean number of wheals (MNW) score, daily mean total symptom score (MTSS) (ie, the sum of the wheal and pruritus scores), and mean interference with sleep and daily activities due to urticaria.

Results: All 4 doses of fexofenadine were statistically superior to placebo ($P \leq .0238$) for MPS, MNW score, and MTSS. Patients receiving fexofenadine HCl also experienced significantly less interference with sleep and daily activities than patients receiving placebo ($P \leq .0001$). Efficacy results were similar in the 60-, 120-, and 240-mg groups and were quantitatively better than those in the 20-mg group. Adverse events were mild and occurred with similar incidence in all treatment groups.

Conclusions: Fexofenadine HCl is well tolerated and is statistically superior to placebo in reducing signs and symptoms of CIU and in ameliorating interference with sleep and daily activities due to urticaria. Doses of 60 mg twice a day or greater are most effective. (*J Allergy Clin Immunol* 1999;103:1071-8.)

Key words: Antihistamine, fexofenadine HCl, chronic idiopathic urticaria, pruritus, wheals

An estimated 15% to 20% of the US population experiences urticaria at some time.^{1,2} Three fourths of chronic urticarial episodes fall into the category of chronic idiopathic urticaria (CIU); that is, they are likely to be persis-

Abbreviations used

ANCOVA:	Analysis of covariance
CIU:	Chronic idiopathic urticaria
MNW:	Mean number of wheals
MPS:	Mean pruritus score
MTSS:	Mean total symptom score
SAR:	Seasonal allergic rhinitis

tent (present for more than 6 weeks), and their origin is unknown. CIU is associated with unrelenting itching (pruritus), which can be distressing and debilitating to those with the disease.³ Results of a recent study of quality of life indicated that patients with CIU attribute sleep disturbances, social isolation, altered emotions, and difficulties with activities of daily living to their skin disease.³

The search for an inciting agent is the physician's first priority in the treatment of any type of urticaria. Despite adequate medical history, physical examination, and laboratory analysis, the cause of CIU remains unidentified in more than 95% of patients.^{4,5} Recent research has identified a wheal-producing IgG antibody in the sera of patients with CIU. Thus, there is evidence that an autoimmune process may be of pathogenic significance in a subpopulation of patients.⁶

Although the etiology and pathogenesis of CIU are still under investigation, the edema, erythema, and pruritus associated with CIU are evoked by histamine and other inflammatory mediators released from mast cells in the skin. A perivascular inflammatory infiltrate consisting of mononuclear cells (CD4⁺, lymphocytes, and monocytes), small numbers of neutrophils, and variable numbers of eosinophils is observed, whereas eosinophil major basic protein is demonstrable in two thirds of the subjects.⁷⁻¹⁰ The infiltrate may be initiated by an autoantibody to the IgE receptor in 35% to 45% of patients.¹¹⁻¹³

Current treatment is directed at the alleviation of symptoms: reducing the intensity of itching and decreasing the number and extent of wheals. Because histamine is a major contributor, antihistamines are the first drugs considered when treating patients with CIU.^{5,14-16} Nonsedating antihistamines are preferred because they are more specific H₁-receptor antagonists. Moreover, they do not cross the blood-brain barrier, so they are devoid of the soporific and anticholinergic side effects associated with first-generation antihistamines.⁶

Fexofenadine HCl is a nonsedating, long-acting antihistamine with highly selective peripheral histamine H₁-

From ^athe National Urticaria Research and Treatment Center, Allergy and Asthma Centers of Charleston, PA, Charleston, and ^bHoechst Marion Roussel, Kansas City.

Supported by a research grant from Hoechst Marion Roussel.

Received for publication March 26, 1999; revised July 16, 1999; accepted for publication July 30, 1999.

Reprint requests: Albert F. Finn, Jr, MD, 9165 University Blvd, Charleston, SC 29406-0145.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/1/101984

receptor antagonist activity, developed for the relief of CIU and seasonal allergic rhinitis (SAR). Fexofenadine produces prompt, long-lasting H_1 blockade in skin tissue; a 60-mg dose twice a day (bid) and a single 120-mg dose significantly suppressed histamine-induced wheal and flare reactions for 24 hours compared with placebo.¹⁷ Recent research suggests fexofenadine has anti-inflammatory properties. In human nasal endothelial cells in vitro, fexofenadine attenuated eosinophil chemotaxis and modulated the release of proinflammatory mediators and adhesion molecules.¹⁸

Currently, a 60-mg bid dose of fexofenadine HCl is approved in the United States for the treatment of SAR. Fexofenadine has demonstrated safety and efficacy in treating CIU, and a dose of 180 mg once a day is now approved for treatment of CIU in some European countries.¹⁹ This North American study was designed to assess the clinical efficacy and safety of a range of fexofenadine HCl doses (20, 60, 120, and 240 mg bid) compared with placebo for relief of CIU symptoms.

METHODS

Patients

Male and female patients aged 12 to 65 years with a diagnosis of CIU, which was defined as the presence of urticarial wheals for at least 3 days per week for 6 consecutive weeks before entry, were enrolled. Patients with urticaria associated with an underlying disease (eg, Hodgkin's disease, vasculitis, hyperthyroidism, lupus erythematosus, hepatitis) and patients with physical urticaria due to cold, heat, or sun were excluded from the study. Similarly, persons with urticaria due to medications, insect bites, food, or other known etiology were ineligible. Also excluded were persons with dermatographism as a primary diagnosis; those unresponsive to prior antihistamine treatment; those with malnutrition, drug abuse or alcoholism, blood dyscrasia, malignancy, renal or hepatic insufficiency, malabsorption, or chronic infection; and those with clinically significant psychiatric, cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease. No female patients were pregnant (or likely to become pregnant) or were lactating during the study. All patients gave informed consent to participate in the study.

Study design

This multicenter, double-blind, randomized, placebo-controlled, parallel study began with a 24-hour single-blind placebo lead-in, followed by a 4-week double-blind treatment period. To participate, patients had a minimum of 1 to 5 wheals, confirmed by the investigator, and had moderate to severe itching during the previous 12 hours. Patients were randomized to receive placebo or 20, 60, 120, or 240 mg of fexofenadine HCl each day at 7 AM and 7 PM. Patients assessed urticarial symptom severity reflectively (over the previous 12 hours) and recorded scores in a daily diary just before taking each dose of the study medication. Pruritus severity was rated on a scale of 0 to 4: 0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying and troublesome, may interfere with sleep/daily activities; 3 = severe, very annoying, substantially interfering with sleep/daily activities; and 4 = very severe, warrants a physician visit. Similarly, the number of wheals was rated on a scale of 0 to 4: 0 = none; 1 = 1 to 5 wheals; 2 = 6 to 15 wheals; 3 = 16 to 25 wheals; and 4 = >25 wheals. Patients reported the extent of interference with sleep and normal daily activities (activities were unspecified) due to their skin condition on a scale of 0 to 3: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

The study comprised 3 or 4 site visits (patients who did not meet inclusion criteria were given a second opportunity to qualify 1 to 14 days after the first visit). Dose cards were collected and diary assessments were made at 15 (± 2) and 30 (± 4) days after the beginning of treatment or at early termination. Systemic or topical medications for CIU, other than study treatment, were not permitted. The study protocol was approved by a central institutional review board.

Efficacy measures

All efficacy measures were reported as average daily means (ie, as the average of the mean of AM and PM assessments made each day). The primary efficacy measure was the change in mean pruritus score (MPS) over the 4-week treatment period. Secondary efficacy measures included change from baseline over the 4-week treatment period in mean number of wheals (MNW) score; mean total symptom score (MTSS), calculated as the sum of the MPS and MNW scores; and interference with sleep and daily activities due to urticaria scores. Average MPS, MNW score, and MTSS were also computed for each week of double-blind treatment.

Safety measures

Fexofenadine safety was assessed with adverse event reporting throughout the study and with laboratory tests (eg, hematology, urinalysis) and physical examinations at the first and final visits.

Statistical analyses

Efficacy analyses were performed on the intent-to-treat population, that is, patients with a baseline and at least 1 postbaseline MPS assessment. Safety-evaluable patients comprised those exposed to double-blind medication with at least 1 postbaseline adverse event assessment. All tests were 2-sided, and P values $\leq .05$ were considered significant. Comparability of demographic and baseline characteristics among treatment groups was assessed with the use of the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. An ANCOVA model, including terms for investigative site, treatment, and baseline values (missing values not imputed) was used to analyze primary and secondary efficacy measures. The frequency of adverse events was tabulated for each treatment; no statistical comparisons were made. The correlation between a dose of fexofenadine HCl and change from baseline in clinical laboratory findings was assessed using the Spearman rank correlation coefficient. Changes from baseline in vital signs were compared across treatment groups using an ANOVA model with the treatment group as a factor.

RESULTS

Of 476 patients from 35 investigative sites who were randomized to study medication, 439 patients (92%) were eligible for inclusion in efficacy analyses (ie, had baseline and at least 1 postbaseline 12-hour reflective MPS assessment). The safety-evaluable population included 455 patients. There were 103 randomized patients (22%) who discontinued the study early (Table I). The rate of early discontinuation was inversely related to the fexofenadine dose, with the highest frequency in the placebo group: 30% versus 26%, 21%, 14%, and 17% in the 20-, 60-, 120-, and 240-mg groups, respectively. The most common reason for early discontinuation was treatment failure (19% in the placebo group versus 11% in the 20-mg group and 5% in the 3 higher-dose groups).

TABLE I. Early discontinuation of randomized patients

Primary reason	Placebo (n = 95)	Fexofenadine HCl (bid)				Total active (n = 381)	Overall total (n = 476)
		20 mg (n = 99)	60 mg (n = 95)	120 mg (n = 95)	240 mg (n = 92)		
Adverse event	5 (5)	5 (5)	5 (5)	3 (3)	1 (1)	14 (4)	19 (4)
Treatment failure	18 (19)	11 (11)	5 (5)	5 (5)	5 (5)	26 (7)	44 (9)
Elected to discontinue	1 (1)	2 (2)	1 (1)	2 (2)	5 (5)	10 (3)	11 (2)
Lost to follow-up	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	2 (1)	3 (1)
Required disallowed medication	1 (1)	0 (0)	3 (3)	2 (2)	1 (1)	6 (1)	7 (2)
Other	2 (2)	8 (8)	5 (5)	1 (1)	3 (3)	17 (5)	19 (4)
Total discontinuations*	28 (30)	26 (26)	20 (21)	13 (14)	16 (17)	75 (20)	103 (22)

Values are expressed as number with percent in parentheses.

*Patients may have had >1 reason to discontinue; only the primary reason is listed here.

TABLE II. Baseline demographics

Characteristics	Placebo (n = 90)	Fexofenadine HCl (bid)				P value
		20 mg (n = 91)	60 mg (n = 86)	120 mg (n = 89)	240 mg (n = 83)	
Sex						
Male	20 (22)	25 (28)	22 (26)	17 (19)	29 (35)	.1677
Female	70 (78)	66 (72)	64 (74)	72 (81)	54 (65)	
Age (yr)						
Mean ± SD	39 ± 13	38 ± 12	38 ± 13	38 ± 12	39 ± 13	.8879
Range	13-67	12-59	12-66	12-65	12-68	
<16 yr	2 (2)	3 (3)	2 (2)	2 (2)	3 (4)	
16-40 yr	42 (47)	46 (51)	49 (57)	44 (49)	37 (45)	
≥40 yr	46 (51)	42 (46)	35 (41)	43 (48)	43 (52)	
Race						
White	83 (92)	84 (92)	75 (87)	80 (90)	73 (88)	.8399
Black	3 (3)	1 (1)	5 (6)	5 (6)	3 (4)	
Asian	3 (3)	4 (4)	4 (5)	2 (2)	6 (7)	
Multiracial	1 (1)	2 (2)	2 (2)	2 (2)	1 (1)	
Weight (kg)						
Mean ± SD	77 ± 19	74 ± 20	76 ± 19	75 ± 20	76 ± 21	.8281
Range	47-136	33-126	32-136	34-130	37-143	

Values are expressed as number with percent in parentheses.

There were no statistically significant differences among treatment groups in baseline demographic characteristics (Table II). For baseline symptom assessments, there was a statistically significant difference among treatment groups in interference with normal activity due to urticaria, with higher scores in the 120-mg group (Table III). This difference did not affect treatment comparisons because all analyses were adjusted for baseline imbalances.

Efficacy

Results of the primary efficacy analysis showed each of the 4 doses of fexofenadine to be statistically superior to placebo ($P \leq .0001$) in reducing MPS, with a significant linear trend for improvement with an increasing dose of fexofenadine ($P = .0001$). Larger reductions from baseline in MPS were observed in the 60-mg group (-1.07) than were observed in the 20-mg group (-0.88), whereas reductions in the 60-mg group were similar to those reported in the 120- and 240-mg groups (-1.07 and -1.18 , respectively, Fig 1). These changes reflect reduc-

tions in pruritus severity of 24% in the placebo group and 48%, 54%, 52%, and 65% in the 20-, 60-, 120-, and 240-mg groups, respectively. There was no significant subgroup (age, weight, race, sex, site) effect on treatment response (data not shown). Covariate analysis showed that patients with higher baseline MPS were likely to report larger reductions in pruritus scores.

Results of secondary efficacy analyses mirrored those of the primary analysis. All doses of fexofenadine HCl showed statistical superiority to placebo during each study week for changes in MPS (Table IV). Moreover, all doses of fexofenadine significantly reduced the MNW score over the 4-week study compared with placebo ($P \leq .0238$), again with a dose-related trend for improvement ($P = .0001$, (Fig 2). In weekly analyses, the 60-, 120-, and 240-mg doses were statistically superior to placebo in reducing the MNW score during each study week; however, the difference between the 20-mg dose and placebo was statistically significant only at the first and fourth weeks.

Fig 3 shows the change in the average MTSS from

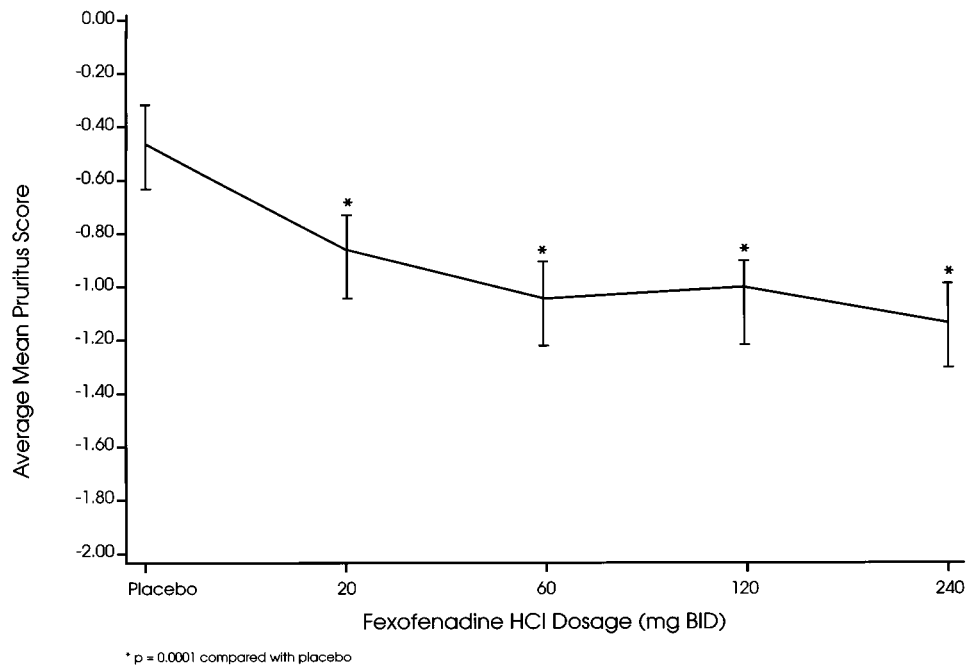


FIG 1. Change (± SE) from baseline in MPS.

TABLE III. Baseline symptom assessments

Symptom measures	Placebo (n = 90)	Fexofenadine HCl (bid)				P value
		20 mg (n = 91)	60 mg (n = 86)	120 mg (n = 89)	240 mg (n = 83)	
MPV						
Mean ± SD	1.9 ± 0.9	1.9 ± 0.9	2.0 ± 0.9	2.0 ± 0.9	1.8 ± 0.7	.2692
Range	0-4	0-4	0-4	0-4	0-4	
MNW score						
Mean ± SD	2.4 ± 1.2	2.4 ± 1.2	2.5 ± 1.2	2.6 ± 1.2	2.4 ± 1.1	.7290
Range	0-4	0-4	0-4	0-4	1-4	
MTSS						
Mean ± SD	4.4 ± 1.8	4.2 ± 1.9	4.4 ± 1.8	4.6 ± 1.9	4.2 ± 1.6	.3874
Range	0-8	0-8	0-8	0-8	1-7	
Interference with sleep						
Mean ± SD	1.2 ± 1.10	1.2 ± 1.1	1.3 ± 1.20	1.5 ± 1.1	1.2 ± 1.0	.3070
Range	-3	0-4	-4	0-3	0-3	
Interference with daily activities						
Mean ± SD	1.2 ± 1.1	± 1.0	± 1.0	1.5 ± 0.9	± 0.9	.0319
Range	0-3	0-3	0-3	0-3	0-3	

baseline with treatment over the 4-week study. All doses of fexofenadine HCl were statistically superior to placebo ($P \leq .0010$). Similarly, all fexofenadine HCl dose groups were significantly superior to placebo ($P \leq .0001$) for mean interference with sleep and daily activities due to urticaria, with a significant linear trend with dose ($P = .0001$, Fig 4).

Safety

Adverse events were reported with similar incidence in all treatment groups (Table V). Nineteen patients discontinued use because of adverse events: 5 patients in the

placebo group and 5 patients in the 20-mg group, 5 patients in the 60-mg group, 3 patients in the 120-mg group, and 1 patient in the 240-mg group. The most commonly reported adverse event was headache. There were no dose-related trends in incidence of any adverse event. The incidence of upper respiratory infection in the 120-mg group was approximately twice that in the other dose groups. This finding is likely to be anomalous, because no correlation between fexofenadine and respiratory infection has ever been observed previously. One serious adverse event was reported: a patient in the 60-mg group was hospitalized for nausea and vomiting resulting from

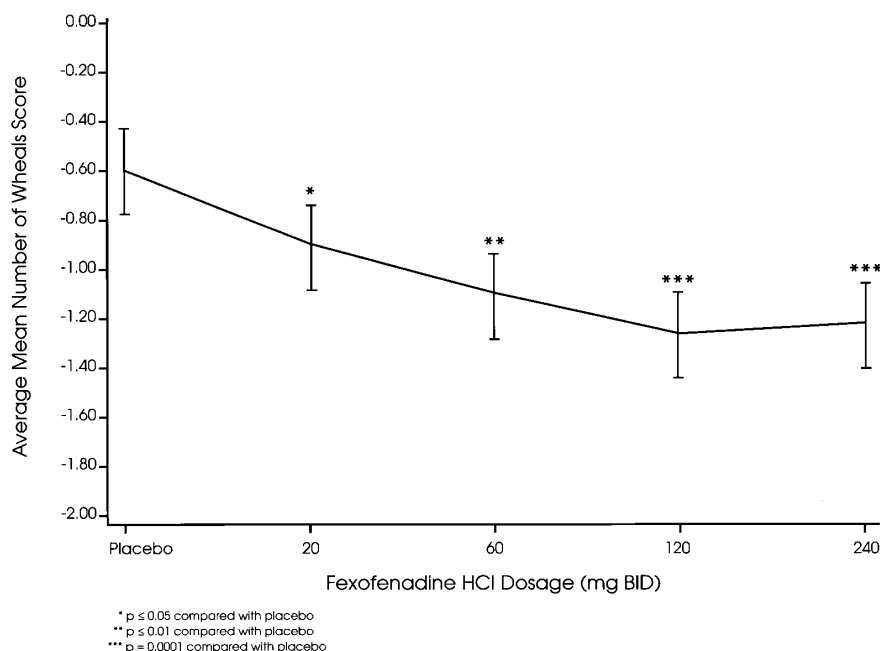
FIG 2. Change ($\pm$ SE) from baseline in MNW score.

TABLE IV. Weekly changes from baseline in MPS

	Placebo	Fexofenadine HCl (bid)				P value
		20 mg	60 mg	120 mg	240 mg	
Week 1, N	90	91	86	89	83	
Mean $\pm$ SE	-0.37 ± 0.07	-0.74 ± 0.07	-0.99 ± 0.07	-0.99 ± 0.07	-1.10 ± 0.07	.0001
Week 2, N	78	81	79	86	80	
Mean $\pm$ SE	-0.59 ± 0.08	-0.92 ± 0.07	-1.09 ± 0.07	-1.07 ± 0.07	-1.17 ± 0.07	.0001
Week 3, N	71	75	75	83	78	
Mean $\pm$ SE	-0.69 ± 0.08	-1.03 ± 0.08	-1.09 ± 0.08	-1.07 ± 0.08	-1.16 ± 0.08	.0003
Week 4, N	66	73	72	80	76	
Mean $\pm$ SE	-0.72 ± 0.09	-1.17 ± 0.08	-1.15 ± 0.08	-1.13 ± 0.08	-1.29 ± 0.08	.0001

a hiatal hernia. The event was considered unrelated to the study medication. Changes in laboratory values and vital signs were unremarkable and were similar among treatment groups.

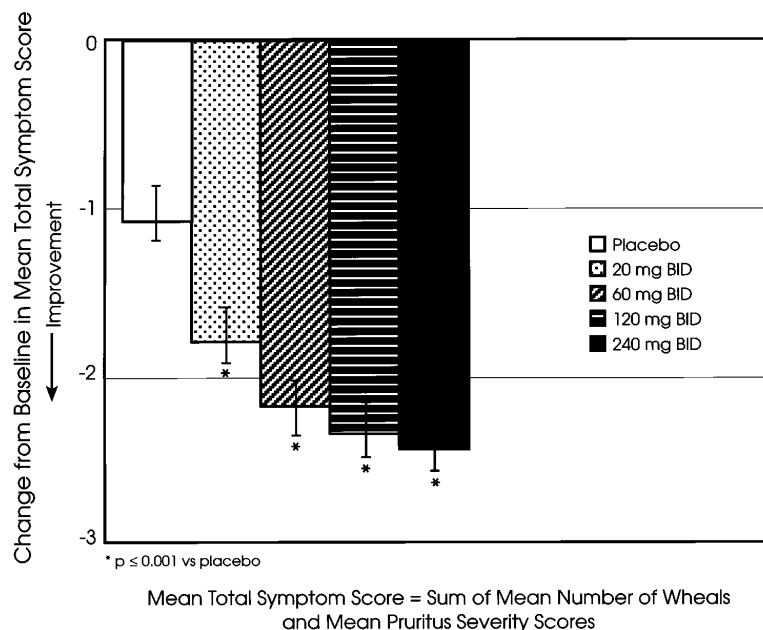
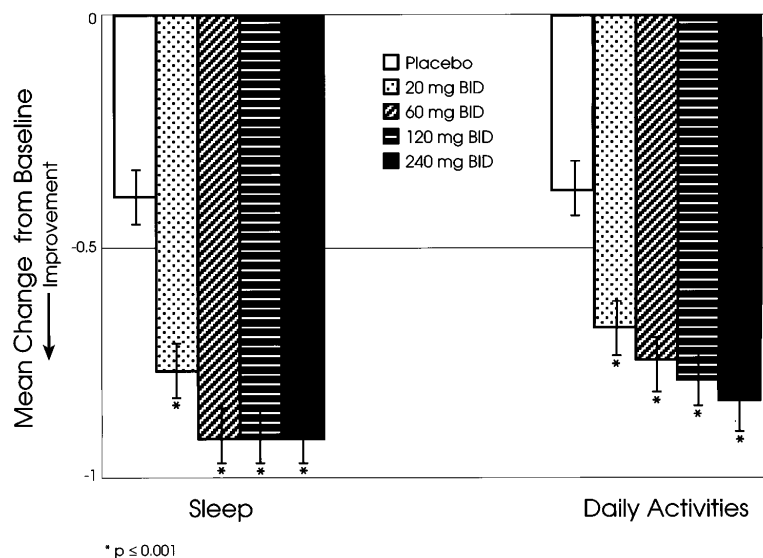
DISCUSSION

The physician's goal is to provide an effective therapy that is safe for the duration of symptomatic CIU. The average length is 6 months, but it may persist for several years.² Doses of fexofenadine HCl at 20, 60, 120, and 240 mg bid significantly relieved pruritus severity and reduced the number of wheals in patients with CIU compared with placebo over a 4-week treatment period, with no evidence of tolerance or loss of effectiveness over time. Fexofenadine treatment significantly reduced patients' MNW scores compared with placebo; in general, antihistamines tend to have little effect on wheals.¹⁴ All doses of fexofenadine were safe and well tolerated, with no dose-related trends in adverse events.

Results of this study concur with previous findings that fexofenadine has a safety profile similar to that of placebo.²⁰⁻²²

Although all doses of fexofenadine gave patients significant relief of CIU symptoms compared with placebo, dose-related trends in efficacy suggest that a 20-mg dose bid of fexofenadine is suboptimal. For example, the percentage of patients who discontinued use because of treatment failure fell from 19% in the placebo group to 11% in the 20-mg group and to only 5% in each of the 3 higher-dose groups. Additionally, fexofenadine at 60 mg bid had a larger treatment effect than 20 mg bid for all efficacy measures. In contrast, the dose of fexofenadine at 60 mg bid had a similar effect in alleviating pruritus severity to that of the 120- and 240-mg bid doses. There was slight improvement in the MNW score and the MTSS in the 2 higher-dose fexofenadine groups compared with the 60-mg group, although the differences were not statistically significant.

As in other chronic diseases, the symptoms of CIU can

FIG 3. Change ($\pm$ SE) from baseline in MTSS.FIG 4. Change ($\pm$ SE) from baseline in mean interference with sleep and daily activities due to wheals.

be so distressing that a considerable number of patients have mild psychopathology as a consequence of their disease.²³ In one of the first studies to measure the effects of CIU on quality of life, patients described cutaneous swelling, itching, and pain, as well as the unpredictable nature of the attacks and social restrictions, among the worst aspects of their skin disease.³ The effect of fexofenadine on the quality of life of patients with CIU is of interest. In this trial, patients receiving fexofenadine HCl reported statistically significant less interference of daily activities and of sleep due to urticaria than did patients taking placebo (Fig 4). Although measurement of these

parameters was not sophisticated, these findings are consistent with preliminary data from 2 double-blind, randomized, health outcomes studies of fexofenadine treatment in patients with CIU that used disease-specific, validated instruments (the Dermatology Life Quality Index and the Work Productivity and Activity Impairment instrument).²⁴⁻²⁶ In those studies, fexofenadine treatment (the same 4 doses used in this trial) was associated with significantly improved quality of life and reduced work and activity impairment compared with placebo in patients with CIU.²⁴

In conclusion, 4 oral doses of fexofenadine HCl at 20,

TABLE V. Most frequently reported ($\geq 2\%$) adverse events

	Placebo (n = 93)	Fexofenadine HCl (bid)				Total (n = 362)
		20 mg (n = 95)	60 mg (n = 89)	120 mg (n = 93)	240 mg (n = 85)	
Total occurrence*	61 (66)	67 (71)	51 (57)	60 (65)	50 (59)	228 (63)
Headache	17 (18)	25 (26)	12 (14)	19 (20)	13 (15)	69 (19)
Dizziness	1 (1)	2 (2)	2 (2)	4 (4)	2 (2)	10 (3)
Upper respiratory infection	7 (8)	5 (5)	5 (6)	16 (17)	7 (8)	33 (9)
Pharyngitis	7 (8)	8 (8)	4 (5)	2 (2)	6 (7)	20 (6)
Rhinitis	6 (7)	6 (6)	4 (5)	1 (1)	2 (2)	13 (4)
Sinusitis	2 (2)	3 (3)	2 (2)	3 (3)	1 (1)	9 (3)
Nausea	4 (4)	6 (6)	1 (1)	5 (5)	6 (7)	18 (5)
Dyspepsia	5 (5)	6 (6)	0 (0)	6 (7)	3 (4)	15 (4)
Diarrhea	5 (5)	3 (3)	3 (3)	1 (1)	1 (1)	8 (2)
Pain	8 (9)	3 (3)	3 (3)	3 (3)	3 (4)	12 (3)
Influenza	4 (4)	6 (6)	4 (5)	5 (5)	6 (7)	21 (6)

Values are expressed as number with percent in parentheses.

*Includes adverse events not listed in this table.

60, 120, and 240 mg bid significantly reduced pruritus severity and decreased the number of urticarial wheals in patients with CIU. Results of this study suggest fexofenadine 60 mg bid has a larger treatment effect than fexofenadine 20 mg bid. There appears to be only slight further improvement in treatment effect with doses of fexofenadine HCl at 120 and 240 mg bid. All doses were well tolerated, with safety profiles similar to that of placebo.

In addition to the authors, study investigators included James W. Baker, MD, Portland, Ore; William E. Berger, MD, Mission Viejo, Calif; Edwin A. Bronsky, MD, Salt Lake City, Utah; Thomas Casale, MD, Papillion, Neb; Paul Chevinsky, MD, North Dartmouth, Mass; John Condemi, MD, Rochester, NY; David Cross, MD, Calgary, Alberta; Jerry Dolovich, MD, Hamilton, Ontario; Donald J. Dvorin, MD, Forked River, NJ; Mark S. Dykewicz, MD, St Louis, Mo; Constantine J. Falliers, MD, Denver, Colo; John W. Georgitis, MD, Winston-Salem, NC; Pinkus Goldberg, MD, Indianapolis, Ind; Alan Goldsobel, MD, San Jose, Calif; Gregory M. Gottschlich, MD, Cincinnati, Ohio; Gary N. Gross, MD, Dallas, Tex; Jacques Hebert, MD, Ste-Foy, Quebec; William C. Howland III, MD, Austin, Tex; Charles Jaffe, MD, Oceanside, Calif; David M. Lang, MD, Philadelphia, Pa; Michael Lawrence, MD, Taunton, Mass; Eugene W. Monroe, MD, Milwaukee, Wis; Robert A. Nathan, MD, Colorado Springs, Colo; Piyush R. Patel, MD, Mississauga, Ontario; Jacob L. Pinnas, MD, Tucson, Ariz; Bruce M. Prenner, MD, San Diego, Calif; Gordon D. Raphael, MD, Bethesda, Md; Paul H. Rainer, MD, San Antonio, Tex; Toivo E. Rist, MD, Knoxville, Tenn; Eric J. Schenkel, MD, Easton, Pa; Guy A. Settipane, MD, Providence, RI; William N. Sokol, MD, Newport Beach, Calif; William E. Stricker, MD, Jefferson City, Mo; Gordon L. Sussman, MD, Toronto, Ontario; Eduardo H. Tschen, MD, Albuquerque, NM; Jeffrey A. Wald, MD, Overland Park, Kan; Stephen C. Weisberg, MD, Minneapolis, Minn; John A. Yarbrough, MD, Gainesville, Ga. Thanks to Sheila Owens for assistance in the development of this manuscript.

REFERENCES

- Greaves MW. Chronic urticaria. *N Engl J Med* 1995;322:1767-72.
- Fox RW. Update on urticaria and angioedema (hives). *Allergy Proc* 1995;16:289-92.

- O'Donnell BF, Lawler F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on quality of life. *Br J Dermatol* 1997;136:197-201.
- Leung DYM, Diaz LA, DeLeo V, Soter NA. Allergic and immunologic skin disorders. *JAMA* 1997;278:1914-23.
- Charlesworth EN, editor. The spectrum of urticaria. *Immunol Allergy Clin North Am* 1995;15:641-56.
- Kobza Black A. The pathogenesis of urticaria. *Keio J Med* 1997;46:37-9.
- Natbony SF, Philips ME, Elias JM, Godfrey HP, Kaplan AP. Histologic studies of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1983;71:177-83.
- Elias J, Boss E, Kaplan AP. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T-lymphocytes, monocytes, and mast cells. *J Allergy Clin Immunol* 1986;87:914-8.
- Sabroe RA, Puon E, Orchard GE, Lane D, Francis DM, Barr RM, et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti FceRI or anti IgE autoantibodies. *J Allergy Clin Immunol* 1999;103:484-93.
- Peters MS, Schrueter AL, Kephart GM. Localization of eosinophil granule major basic protein in chronic urticaria. *J Invest Dermatol* 1983;81:39-43.
- Hide M, Francis DM, Grattan CEH, Hakimi JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993;328:1599-1604.
- Ferrer M, Kinet J-P, Kaplan AP. Comparative studies of functional and binding assays for IgG anti FceRI α (α subunit) in chronic urticaria. *J Allergy Clin Immunol* 1998;101:672-6.
- Fiebiger E, Maurer D, Holub H, Reininger B, Hartmann G, Woisetschlager M, et al. Serum IgG autoantibodies directed against the α chain of FceRI: a selective marker and pathogenic factor for a distinct subset of chronic urticaria patients. *J Clin Invest* 1995;96:2606-12.
- Greaves MW, Sabroe RA. ABC of allergies: allergy and the skin. I-urticaria. *BMJ* 1998;316:1147-50.
- Soter NA. Urticaria: current therapy. *J Allergy Clin Immunol* 1990;86:1009-14.
- Greaves MW, Sabroe RA. Histamine: the quintessential mediator. *J Dermatol* 1996;23:735-40.
- Simons FER, Simons KJ. Peripheral H1 blockade of fexofenadine. *Ann Allergy Asthma Immunol* 1997;79:530-2.
- Abdelaziz MM, Devalia JL, Khair MA, Bayram H, Prior AJ, Davies RJ. Effect of fexofenadine on eosinophil-induced changes in epithelial permeability and cytokine release from nasal epithelial cells of patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1998;101:410-20.
- Paul E, Berth-Jones J, Ortonne J-P, Stern M. Fexofenadine hydrochloride in the treatment of chronic idiopathic urticaria: a placebo-controlled, parallel-group, dose-ranging study. *J Dermatol Treat* 1998;9:143-9.
- Bernstein D, Schoenwetter W, Nathan R, Storms W, Ahlbrandt R, Mason J. Efficacy and safety of fexofenadine hydrochloride for treat-

- ment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1997;79:443-8.
21. Bronsky EA, Falliers CJ, Kaiser HB, Ahlbrandt R, Mason J. Effectiveness and safety of fexofenadine, a new nonsedating H1-receptor antagonist in the treatment of fall allergies. *Allergy Asthma Proc* 1998;19:135-41.
 22. Pratt C, Mason J, Russell T, Reynolds R, Ahlbrandt R. Cardiovascular safety of fexofenadine HCl. *Am J Cardiol* 1999;83:1451-4.
 23. Badoux A, Levy DA. Psychologic symptoms in asthma and chronic urticaria. *Ann Allergy* 1994;72:229-34.
 24. Thompson A, Finn A, Schoenwetter W. Effect of 60 mg bid fexofenadine HCl on quality of life, work productivity, and regular activity in patients with chronic idiopathic urticaria [abstract]. *Ann Allergy Asthma Clin Immunol* 1999;82:122.
 25. Finlay AY, Kahn GK. Dermatology Life Quality Index (DLQI)—a simple, practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19:210-6.
 26. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353-65.

Your comprehensive reference to valuable research information...

Now you can have easy access to research information with the five-year cumulative author and subject index to Volumes 87-96 of *The Journal of Allergy and Clinical Immunology*.

The Cumulative Index is your comprehensive reference guide, including a list of every article in the Journal from 1991 through 1995. All articles are indexed both by subject and by author.

The Cumulative Index features:

- Offset and bold Subject Headings that make searching for subject entries easier
- Subject Entries containing complete article title, author(s), year of publication, volume, and page
- Author Entries listing author(s), article title, author-to-author referral, year of publication, volume, and page

Order *The Journal Of Allergy and Clinical Immunology* Cumulative Index today!

M Mosby

YES! Please send me the Five-Year Cumulative Index to *The Journal of Allergy and Clinical Immunology* (1991-1995). I've indicated my method of payment below. All prices include shipping.

☐ \$55.00 U.S. ☐ \$63.66 Canada* ☐ \$59.50 International

*Includes Canadian GST.

Payment must accompany your order.

- ☐ Check enclosed (U.S. funds, payable to *The Journal of Allergy and Clinical Immunology*)
- ☐ Mastercard ☐ Visa ☐ Discover

Credit Card # _____ Exp. Date _____
Signature _____

Name _____
Institution _____
Address _____
City _____ State _____
Zip _____ Country _____

To order, just call
1-800-453-4351

Outside the U.S.: 314-453-4351
Fax: 314-432-1158

Or return coupon to:
Mosby, Inc.
Periodical Subscription Services
11830 Westline Industrial Dr.
St. Louis, MO 63146 U.S.A.

J01976FZ