The Effect of Fexofenadine Hydrochloride on Productivity and Quality of Life in Patients With Chronic Idiopathic Urticaria

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The present study examined the impact of once-daily fexofenadine hydrochloride (HCl) 180 mg on health-related quality of life (HRQL) in subjects with chronic idiopathic urticaria (CIU). This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Subjects completed the Dermatology Life Quality Index (DLQI) and the Work Productivity and Activity Impairment (WPAI) questionnaire at baseline and at weeks 2 and 4. The primary HRQL end point was mean change from baseline to week 4 in total DLQI score. Subjects in the fexofenadine HCl treatment group (n=163) experienced significantly greater improvements in mean total DLQI score (P=.0219) and in the individual domains of symptoms and feelings (P=.0119) and personal relationships (P=.0091) compared with those in the placebo group (n=91). Subjects who received fexofenadine HCl experienced less work productivity impairment, overall work impairment, and activity impairment than those who received placebo. The results indicated that once-daily fexofenadine HCl 180 mg improved the HRQL of subjects with CIU, as assessed by change in total DLQI score.

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Chronic urticaria is characterized by recurring cutaneous wheals that invariably are accompanied by swelling and pruritus. The condition also has a profound negative impact on the health-related quality of life (HRQL) of patients, partially attributed to embarrassment and prejudice. Despite growing awareness of the underlying causes of chronic idiopathic urticaria (CIU), the etiology of the disease remains unknown in most patients. Approximately 35% to 40% of patients with chronic urticaria have autoimmune urticaria,[1-4] whereas the pathogenesis of the remaining 60% to 65% is truly idiopathic. Few well-designed studies have been conducted to evaluate the impact of CIU on HRQL, but from the data available, the erosion of HRQL associated with the disease is substantial.[5]

Fexofenadine is a nonsedating H_1-receptor antagonist that has been shown to be effective and safe for the treatment of CIU.[6] Twice-daily fexofenadine hydrochloride (HCl) 60 mg has been approved in the United States to treat the uncomplicated skin manifestations of CIU in individuals aged 12 years and older. The present report explores the hypothesis that once-daily fexofenadine HCl 180 mg

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improves the HRQL of patients with CIU, and represents the HRQL end points from a previous study that presented efficacy and safety findings.[7]

MATERIALS AND METHODS

Study Population

Males and females aged 12 years and older with a diagnosis of CIU and a history of urticarial wheals for 3 or more days a week for 6 consecutive weeks prior to the first visit were eligible to participate. In addition, subjects were required to have 1 or more wheals and to have reflectively rated their pruritus as 2 or higher on a scale of 0 to 4 (0=none, 4=very severe) during the previous 12 hours. All subjects were required to provide written informed consent. Full details of the study population and study design are presented elsewhere.[7]

Study Design

This multicenter, randomized, double-blind, parallel-group, placebo-controlled study comprised a single-blind placebo run-in period for 2 to 5 days, followed by a 28 (±4)–day double-blind treatment period.[7] The trial was designed to assess the efficacy and safety of a once-daily dosage of fexofenadine HCl 180 mg, with the impact of this dosage on HRQL as a secondary efficacy end point. Efficacy measures of wheal and pruritus were primary end points of the trial and are reported elsewhere.[7]

The impact of urticaria on each subject's HRQL and productivity was assessed using the Dermatology Life Quality Index (DLQI) and the Work Productivity and Activity Impairment (WPAI) questionnaire, which were completed by the subjects at baseline, weeks 2 and 4, or at early termination.

The study complied with the International Conference on Harmonisation Good Clinical Practice guidelines, and the protocol was approved by an independent institutional review board and local institutional review boards, where necessary.

Study Instruments

Dermatology Life Quality Index—The DLQI is a questionnaire with a 10-item scale designed to assess the impact of skin disease on HRQL.[8] It comprises 6 domains: symptoms and feelings; daily activities; leisure; work and school; personal relationships; and treatment. Questions are scored from 0 to 3 (0=not at all/not relevant/question not answered, 1=a little, 2=a lot, 3=very much [maximum score, 30]). Total scores and subscores for each domain are calculated, with higher scores indicating greater impairment.

WPAI Questionnaire—The WPAI is a 6-item questionnaire that was developed to measure work productivity and activity impairment in clinical trials. The structure of the WPAI questionnaire has been previously reported.[9] Using this assessment, scores for the following 4 parameters can be calculated: the percentage of work time missed because of wheals, percentage of work productivity impairment because of wheals, percentage of overall work impairment because of wheals, and percentage of activity impairment because of wheals.

Analysis Variables—The primary HRQL end point was mean change in total DLQI score from baseline to week 4. Other HRQL end points included mean changes in individual DLQI domain and WPAI scores from baseline to week 4.

Statistical Procedures—Summary statistics were used to provide a general description of the subjects studied and to characterize baseline characteristics. All statistical tests were 2 tailed, and *P* values of .05 were considered statistically significant. Results were based on analysis of data obtained from the intent-to-treat population that completed a baseline and 1 or more follow-up DLQI assessments.

Change from baseline was compared within treatment groups and between fexofenadine HCl and placebo treatment arms using an analysis of covariance model with factors for site and treatment group, and (pooled) site and baseline scores as covariates. In a preliminary model of change from baseline in total DLQI score, the treatment-by-baseline interaction was significant ($P=.007$), but the treatment-by-site interaction was not significant ($P=.17$). Therefore, only baseline scores were included in the final model.

To further analyze how treatment affected HRQL and productivity during the study period, scores obtained at week 2 were considered by assessing the change from baseline in the unadjusted mean DLQI and WPAI scores calculated from the mean scores from weeks 2 and 4 combined.

Psychometric Properties of the DLQI and WPAI Questionnaires—Additional analyses were conducted to examine the internal consistency reliability, validity, and responsiveness of the HRQL and productivity measures. The internal consistency reliability of the DLQI was established using Cronbach α (a measure of the mean intercorrelation between questions, weighted by variances).[10]

The relationships between DLQI and WPAI scores and clinical outcomes were analyzed to test the validity of the 2 instruments, and the degree of correlation between the 2 instruments was analyzed to establish if they measured related constructs. Furthermore, the extent to which changes in HRQL and productivity scores correlated with changes in clinical outcomes formed the basis of assessment of the responsiveness of the 2 instruments.

Total DLQI Score and WPAI Questionnaire Subscale Scores for the HRQL Treated Population*

Baseline Parameter	Placebo	Fexofenadine HCl	N=254	*P* Value
Total DLQI score				
No. of subjects	91	163	254	
Mean (SD)	10.5 (6.4)	11.3 (6.4)	11.1 (6.3)	.328
Work time missed (WPAI)				
No. of subjects	69	120	189	
Mean (SD)	3.4 (8.6)	4.2 (11.5)	3.9 (10.5)	.636
Work productivity impairment (WPAI)				
No. of subjects	71	120	191	
Mean (SD)	32.1 (24.2)	34.4 (23.4)	33.6 (23.7)	.517
Overall work impairment (WPAI)				
No. of subjects	69	118	187	
Mean (SD)	33.4 (25.7)	35.8 (25.0)	34.9 (25.2)	.526
Activity impairment (WPAI)				
No. of subjects	91	161	252	
Mean (SD)	36.0 (25.7)	39.9 (26.1)	38.5 (25.9)	.253

*DLQI indicates Dermatology Life Quality Index; WPAI, Work Productivity and Activity Impairment; HRQL, health-related quality of life.

RESULTS

Subjects

Two hundred fifty-five subjects were included in the intent-to-treat population, of which 254 completed a baseline and 1 or more follow-up HRQL assessments. Of these, 163 subjects (64%) were randomized to treatment with fexofenadine HCl and 91 subjects (36%) to treatment with placebo. There were no significant differences at baseline between treatment groups in terms of demographic variables (not shown), severity of CIU, total DLQI score, or responses to the WPAI questionnaire (Table).

DLQI Assessments

Improvements from baseline in total DLQI score to week 4 were observed with fexofenadine HCl and placebo. Subjects in the fexofenadine HCl treatment group experienced significantly greater improvements from baseline in mean total DLQI score compared to the placebo treatment group (6.2 vs 4.7, respectively [95% CI, 0.2 and 2.9, respectively]; $P=.0219$).

Subjects receiving fexofenadine HCl experienced greater improvements in each of the individual domains of the DLQI from baseline to week 4 compared with subjects receiving placebo, though both treatment groups experienced improvements from baseline. Improvements from baseline were significantly greater in the fexofenadine HCl treatment group compared with the placebo treatment group for the individual domains of symptoms and feelings (1.9 vs 1.4, respectively [95% CI, 0.1 and 0.9, respectively]; $P=.0119$) and personal relationships (0.7 vs 0.3, respectively [95% CI, 0.1 and 0.6, respectively]; $P=.0091$).

When the unadjusted means of weeks 2 and 4 scores combined were examined, subjects receiving fexofenadine HCl experienced significantly greater improvements from baseline in mean total DLQI score than those receiving placebo (6.07 vs 3.91, respectively; $P=.0029$). Furthermore, improvements from baseline were significantly greater in the fexofenadine HCl treatment group compared with the placebo treatment group for the domains of symptoms and feelings

(1.80 vs 1.23; $P=.0071$), daily activities (1.36 vs 0.88; $P=.013$), leisure (1.07 vs 0.70; $P=.0425$), and personal relationships (0.71 vs 0.23; $P=.0023$).

WPAI Questionnaire Assessments

Both treatment groups reported improvements in productivity (change from baseline to week 4) using the WPAI questionnaire. However, the magnitude of improvement was greater for subjects receiving fexofenadine HCl than for those receiving placebo, as assessed by work productivity impairment, overall work impairment, and activity impairment.

When the unadjusted scores from weeks 2 and 4 combined were analyzed, subjects receiving fexofenadine HCl compared with placebo experienced significantly less work productivity impairment (improvement from baseline, 18.45 vs 11.76, respectively; $P=.0455$) and activity impairment (improvement from baseline, 22.11 vs 13.96, respectively; $P=.0088$).

Psychometric Evaluations

Responses for each item of the DLQI spanned the full range of possible scores at each assessment, suggesting that the DLQI was relevant to this population sample. At baseline and throughout the study, items directly addressing the condition of the skin had a greater impact than items addressing sexual difficulties and relationship problems. In general, the administration of treatment of urticaria did not appear to impact HRQL, as evidenced by responses to the treatment subscale of the DLQI (54% of subjects responded that treating their CIU was not a problem). Only the item "How itchy, sore, painful, or stinging has your skin been?" was not associated with the full range of responses at baseline; no subjects answered "not at all," confirming that all subjects had active disease at baseline.

Responses for the WPAI questionnaire spanned the full range of possible scores for work time missed, work productivity impairment, overall work impairment, and activity impairment because of wheals, indicating the relevance of this instrument to the 76% of subjects (n=193) who were employed at baseline. However, at baseline, only 1 of 191 employed subjects who responded reported that they were prevented from working the previous week because of wheals. Conversely, 79% of subjects reported no time from work was missed because of wheals.

Internal Consistency Reliability—The Cronbach α for total DLQI score was 0.87, indicating 87% internal consistency reliability, whereas 70% usually is considered adequate.[10]

Validity—Both the total DLQI score and individual domain scores significantly correlated with WPAI measures of work time missed, work productivity impairment, overall work impairment, and activity impairment ($P<.001$ for all correlations at baseline), indicating that the DLQI and WPAI instruments measured related constructs. Correlation coefficients were positive, showing that subjects with severe HRQL impairment at baseline were less productive.

In addition, most DLQI and WPAI scores correlated significantly with the clinical measures of number of lesions, frequency of episodes, average size of lesions, severity of pruritus, and total symptom score (sum of lesions and pruritus severity)($P<.05$ for 57 of 66 comparisons).

Responsiveness—Most changes in DLQI domain and WPAI scores from baseline to week 4 were significantly correlated with changes in clinical measures ($P<.05$). The weakest correlations with clinical changes were observed with the DLQI domain of treatment and the WPAI item of work time missed. Similarly, all changes in HRQL and productivity outcome scores significantly correlated with subject-assessed global evaluations of change in CIU ($P\leq.01$), with the exception of work time missed because of wheals. When the same analysis was performed using physician-assessed global evaluations of change in CIU status, all HRQL changes significantly correlated with changes in global evaluations ($P\leq.05$).

COMMENT

Treatment of CIU with once-daily fexofenadine HCl 180 mg significantly improved HRQL of subjects compared with placebo ($P=.0219$), as assessed by the change in total DLQI score from baseline to week 4. In addition, subjects randomized to fexofenadine experienced statistically significant improvements compared with placebo for the DLQI domains of symptoms and feelings ($P=.0119$) and personal relationships ($P=.0091$). Improvements in DLQI in the fexofenadine HCl treatment group were associated with trends in improved productivity at work, less overall work impairment, and less activity impairment, as assessed by changes in the WPAI. Assessments performed at week 2 demonstrated that treatment with fexofenadine significantly improved subject outcome in 4 of 6 DLQI domains ($P<.05$) and 2 of 4 WPAI evaluations ($P<.05$).

Areas in which improvements were less pronounced were the domains of work and school, and treatment as assessed by the DLQI, and work time missed because of wheals as measured by the WPAI questionnaire. At baseline, missing time from work

was not an issue for most subjects (median hours missed over previous week at baseline, 0); therefore, effective treatment was unlikely to affect this parameter as evidenced by both the DLQI and WPAI questionnaires. Similarly, 53.9% of subjects reported no difficulties in treating their CIU at baseline, suggesting high levels of acceptance of treatment that were unlikely to improve with continued treatment.

Both the DLQI and WPAI assessment tools have been validated for use in clinical trials[8,11]; furthermore, in 2004, the DLQI was proved as a valid instrument for use in CIU populations.[12] In the present study, the DLQI was reliable in terms of its internal consistency, and the DLQI and WPAI questionnaires correlated with each other, suggesting that both instruments measured related constructs. Clinical symptoms correlated with HRQL, and the instruments were sensitive enough to detect changes in clinical status. With the internal consistency reliability, validity, and responsiveness of these instruments confirmed, these HRQL results can be interpreted with confidence.

The results presented here corroborate those of previous studies. For example, studies by Finn et al[13] and Nelson et al[14] examined the effect of twice-daily fexofenadine HCl 20, 60, 120, and 240 mg or placebo on interference with sleep and daily activities. Both studies were conducted over 4 weeks, and responses were measured on a 4-point scale (0=none, 3=severe). Overall, subjects receiving fexofenadine HCl experienced significantly less interference with sleep and daily activities than those administered placebo ($P \leq .0014$[14] and $P \leq .0001$,[13] respectively). In another study, once-daily fexofenadine HCl 60, 120, 180, and 240 mg were examined using the same 4-point scale.[15] All dosages of fexofenadine HCl showed greater improvements in sleep quality and less interference with daily activities than placebo ($P < .05$ for all comparisons).

The effect of twice-daily dosages of fexofenadine HCl 60 mg also has been evaluated in 2 identical 4-week, placebo-controlled, multicenter studies that used the DLQI and WPAI questionnaire to assess HRQL.[16] Significantly greater improvements from baseline to end of study in adjusted total DLQI scores for fexofenadine HCl were observed versus placebo ($P \leq .0002$). Significant improvements also were noted for 5 of 6 domains of the DLQI ($P < .05$). Positive results for fexofenadine HCl also were noted in terms of increased work productivity ($P \leq .0152$) and performance of daily activities ($P \leq .0002$).[16]

CONCLUSION

These findings show that once-daily fexofenadine HCl 180 mg improved the HRQL of subjects with CIU after 4 weeks of treatment, as assessed by change in total DLQI score. Optimal treatment of CIU should target the substantive relief of wheal and pruritus as well as the additional patient-assessed benefit of improved quality of life.

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