

Model for outcomes assessment of antihistamine use for seasonal allergic rhinitis

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Background: Drug selection for optimal treatment of common medical conditions may be difficult and involve many diverse factors.

Objective: The efficacy, safety, quality of life, and cost of treatment of seasonal allergic rhinitis with cetirizine, chlorpheniramine, or terfenadine were compared in a prospective, two-phase, randomized, single-blind clinical trial conducted in a managed care setting.

Methods: In phase I, which lasted 2 weeks, patients were randomized to receive one of the study drugs. In phase II, which lasted 4 weeks, the initial treatment was continued unless patients were dissatisfied, in which case they could be randomly assigned to receive another study drug. In both phases pseudoephedrine could be taken as needed. Patients kept daily diaries of symptoms and costs, and study drugs were evaluated at the end of each phase for efficacy, safety, and effect on quality of life by means of a validated questionnaire. A multiattribute outcomes assessment model for formulary decision making was used to rank the antihistamines.

Results: Physicians' and patients' assessments in phases I and II indicated that cetirizine and chlorpheniramine were significantly more effective than terfenadine ($p < 0.05$). Incidence of sedation in phase I and phase II was 40.5% and 16.7% for chlorpheniramine, 11.6% and 9.8% for cetirizine, and 6.7% and 5.1% for terfenadine, respectively. At the end of phase I, 28.9% of the patients treated with chlorpheniramine, 50% of the patients treated with terfenadine, and 69.4% of the patients treated with cetirizine were satisfied with their therapy and chose not to switch their medication. Quality of life scores improved most after treatment with cetirizine and least after treatment with terfenadine.

Conclusion: The results of this trial indicate that antihistamine selection is best made with the use of a multiattribute evaluation that includes quality of life. In this study cetirizine was favored by patients and physicians most often, followed by chlorpheniramine and then terfenadine. (*J Allergy Clin Immunol* 1996;97:1233-41.)

Key words: Rhinoconjunctivitis, quality of life, cetirizine, terfenadine, chlorpheniramine, cost, managed care, multiattribute, efficacy

Seasonal allergic rhinitis (SAR) affects more than 50 million Americans and is associated with significant morbidity. The direct costs of allergic

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Abbreviations used

MAUT: Multiattribute utility theory
RQLQ: Rhinoconjunctivitis quality-of-life questionnaire
SAR: Seasonal allergic rhinitis

rhinitis include annual drug expenditures of \$2 billion; indirect costs are estimated to include 28 million days of restricted activity and 2 million lost school days annually.¹

Antihistamines are a mainstay of SAR therapy. First-generation antihistamines such as chlor-

pheniramine, diphenhydramine, and doxylamine relieve SAR symptoms but cause central nervous system side effects such as sedation and impaired psychomotor activity in approximately 20% of patients.² Further, a lack of perceived drowsiness associated with first-generation antihistamines may not correlate with measures of central nervous system impairment; for example, patients taking these antihistamines may be more impaired than they realize.^{3, 4}

The development of newer antihistamines marked a major advance in the treatment of SAR. The newer H₁-selective antihistamines such as cetirizine, astemizole, loratadine, and terfenadine relieve SAR symptoms but have lower incidences of somnolence and do not impair psychomotor performance.³⁻¹⁰

Within managed care organizations, formulary medication choices are often made only on the bases of efficacy, safety, and cost. Despite increased sedation, first-generation antihistamines are selected more frequently because they are less expensive and their side effects are not considered life-threatening. However, when the impact of sedation on quality of life and additional factors are considered, the newer antihistamines may be favored.

An evaluation called the multiattribute utility theory (MAUT) facilitates the prioritization of advantages and disadvantages of treatments, thereby providing a framework for integrating diverse outcomes into one decision hierarchy.¹¹ The MAUT, together with a rhinoconjunctivitis quality-of-life questionnaire (RQLQ), which is a disease-specific, validated, reproducible instrument to evaluate quality of life on the basis of how the symptoms and treatment affect a patient's physical and emotional functioning, provide more pertinent information for making antihistamine choices.¹²

This study used MAUT and RQLQ in conjunction with efficacy, safety, and cost of cetirizine, chlorpheniramine, and terfenadine therapy in patients with SAR to analyze antihistamine use outcome and simulate formulary decision-making processes.

METHODS

This study was a prospective, multicenter, randomized, investigator-blinded, parallel-group, two-phase trial conducted during the ragweed pollen season. During phase I, which lasted 2 weeks, patients were randomized to treatment with cetirizine (5 to 10 mg every day), chlorpheniramine (4 mg three or four times daily), or terfenadine (60

mg twice daily). Patients were allowed to add pseudoephedrine (60 mg three or four times daily). For the 4-week, second phase of this study, patients and their physicians determined either to continue the current study medications or, if patients were dissatisfied with their current treatment, to randomize them to receive one of the two alternative treatments. During the second phase, intranasal cromolyn sodium and beclomethasone were allowed.

METHODS

Patients

Male and female subjects aged 16 years or older who had a documented history of SAR and were otherwise in good health were considered for enrollment. Participants had three or more of the following symptoms of moderate severity: postnasal drip, watery nasal discharge, sneezing, itchy nose, nasal congestion, watery eyes, and itchy eyes. Participants also had a positive skin test response to ragweed, pigweed, kochia, Russian thistle, or sage.

Patients were excluded from the study if they were hypersensitive to antihistamines or had been treated with antihistamines or decongestants within 72 hours, with astemizole within 56 days, or with corticosteroids within 30 days of beginning the trial. Patients who had been treated with corticosteroids and antihistamines for 3 or more consecutive weeks or who had received immunotherapy within 3 years of the study were excluded. Patients were also excluded if they had child-bearing potential and were not using an adequate form of birth control, were pregnant, or were breast-feeding.

The study protocol was approved by the institutional review board at each site, and all patients gave written, informed consent.

Procedures

The trial was divided into phase I, which lasted 2 weeks, and phase II, which lasted 4 weeks. Patients were evaluated at three visits. Visit 1 marked the beginning of phase I, visit 2 marked the end of phase I and the beginning of phase II, and visit 3 marked the end of phase II.

Patients' and physicians' assessments, RQLQ, and pertinent laboratory tests were performed at each visit. During phase II, patients continued their treatment or changed to one of the other randomly assigned study medications. Symptom diaries were evaluated at visits 2 and 3.

Outcome measures

Patient compliance. Patient compliance was evaluated at visits 2 and 3. It was determined by medication counts, which were correlated with dosing information recorded in the patients' diaries.

Efficacy. Using a 10-point scale (0 = complete absence of symptoms, 9 = unbearable symptoms), patients recorded in diaries each day, at the time of their

TABLE I. Demographic characteristics of enrolled patients

Characteristic	Cetirizine	Chlorpheniramine	Terfenadine	Total
Sex				
Male	19 (44.2%)	17 (39.5%)	16 (35.6%)	52 (39.7%)
Female	24 (55.8%)	26 (60.5%)	29 (64.4%)	79 (60.3%)
Age (yr)				
Mean	35.2	34.4	33.7	34.4
Range	16.1-64.6	16.4-68.3	16.0-59.6	16.0-68.3
Race/ethnic group				
White	35 (81.4%)	32 (74.4%)	38 (84.4%)	105 (80.1%)
Black	2 (4.7%)	4 (9.3%)	3 (6.7%)	9 (6.9%)
Hispanic	5 (11.6%)	5 (11.6%)	1 (2.2%)	11 (8.4%)
Other	1 (2.3%)	2 (4.7%)	3 (6.7%)	6 (4.6%)

morning dose, their SAR symptom severity (postnasal drip, runny nose, sneezing, itchy nose, nasal congestion, watery eyes, and itchy eyes) for the previous 24 hours. Physicians and patients recorded SAR symptom severity by using the same 10-point scale. At visits 2 and 3, patients and physicians completed global assessments of the efficacy of treatment for rhinitis by using a 5-point scale (1 = excellent control of symptoms, 5 = poor control of symptoms). Patients also rated their overall satisfaction with treatment by using a 5-point scale (1 = exceptionally satisfied, 5 = dissatisfied). If additional medication was needed, it was noted at these visits.

Quality of life. At visits 1, 2, and 3, patients assessed quality of life by completing the RQLQ.¹² The survey included 28 questions in seven variable groups that measured each patient's subjective experience of rhinoconjunctivitis symptoms and their effect on his or her quality of life. Physical symptoms were measured on a 7-point scale (0 = not troubled, 6 = extremely troubled), and emotional symptoms were also measured on a 7-point scale (0 = troubled none of the time, 6 = troubled all the time).

Safety. Information regarding adverse events was collected through medical history, physical examination, laboratory testing, inquiry, and observation. The nature, incidence, and severity of any adverse events were recorded.

Costs. Direct and indirect costs were recorded. Direct costs included nursing and physician time, clinic visit costs, and drug costs. Indirect costs included travel and missed time from work or school.

Statistical methods

Efficacy. A mean daily total symptom severity score was calculated for each day during phase I (excluding nasal congestion), and from scores, a mean total symptom severity score was calculated for phase I. For patients' ratings and physicians' ratings separately, analysis of covariance procedures were used to compare symptom severity between treatment groups, with adjustments for baseline symptom severity as an initial covariate. Analysis of variance procedures were also

used to compare patients' and physicians' global assessments of efficacy between treatment groups. Similar analyses were done for phase II.

Safety. The proportion of patients who reported sedation was compared between treatment groups by using the likelihood ratio chi square statistic. Pairwise comparisons were made by using categorical modeling (SAS PROC CATMOD; SAS Institute, Cary, N.C.).¹³ The incidence of other adverse events was summarized by treatment group.

RQLQ. The quality of life score was computed as the sum of items in each of the seven symptom categories. For phases I and II of the trial, analysis of covariance procedures, as used for efficacy, were used to evaluate the effectiveness of treatment.

Cost. Total direct and indirect organizational and patient costs were determined. However, sparsity of indirect cost data precluded statistical analysis.

MAUT. The MAUT was used to determine the relative value of each treatment.¹¹ The factors included in the analysis—efficacy, safety, cost, compliance, and quality of life—were selected by participating physicians, nurses, and administrators and were then weighted for relative importance and combined into a total utility score. Sensitivity analyses, which evaluated the impact of different values and weights on the total utility score, were then performed.

RESULTS

A total of 131 patients were enrolled in the trial and randomly assigned to receive one of the study medications. Eighty percent of patients were white, and 60% were female; the mean age was 34.4 years. There were no significant demographic differences between treatment groups (Table I). Of the 131 patients who entered phase I, 130 received medication and could be evaluated for treatment safety and 122 could be evaluated for treatment efficacy. Three patients could not be evaluated because of noncompliance, four because of illness,

TABLE II. Distribution of enrolled patients among treatment groups

	Cetirizine	Chlorpheniramine	Terfenadine	Total
Phase I	43	43	45	131
Phase II	51	25	40	116

and one because of protocol violation; one patient was lost to follow-up. Of the 116 patients who entered phase II, 114 could be evaluated for treatment safety, and 111 could be evaluated for treatment efficacy. Two patients could not be evaluated because of illness, two because of protocol violations, and one because of noncompliance. The distribution of enrolled patients among treatment groups is summarized in Table II for each phase of the study.

Efficacy

Phase I. Patients assessed their symptoms at baseline and at the end of 2 weeks of treatment (Table III and Fig. 1). The reduction in SAR symptoms after 2 weeks of treatment showed significant differences between treatment groups for total symptom severity, runny nose, and sneezing. Cetirizine was more effective than terfenadine for reducing total symptom severity and relief of sneezing and runny nose, whereas chlorpheniramine was more effective than terfenadine for reducing the total symptom score and relief of sneezing only.

Physicians' evaluations of SAR, in which total and individual symptom severity scores were used, showed significant differences between treatment groups (Fig. 2). As indicated in Fig. 2, both cetirizine and chlorpheniramine were more effective than terfenadine for reducing the total symptom score.

Phase II. At the beginning of phase II, patients could continue their current therapy, or if dissatisfied, could switch to one of the two alternative treatments for the 4-week treatment period. Almost 29% (28.9%) of the patients treated with chlorpheniramine, 50.0% of the patients treated with terfenadine, and 69.4% of the patients treated with cetirizine were satisfied with their therapy (Fig. 3). Therefore over 70% of patients treated with chlorpheniramine switched their medication. At the end of phase II, patients' evaluations showed significant differences in favor of cetirizine versus terfenadine and chlorpheniramine versus terfenadine for relief of postnasal drip and runny nose (Table III).

Physicians' evaluations of SAR, in which total and individual symptom severity scores were used, showed significant differences between treatment groups (Fig. 2). Both cetirizine and chlorpheniramine were more effective than terfenadine for reducing total symptom severity score.

An average of 13.5% of patients used adjunctive beclomethasone during phase II. Of the patients who continued their initial treatment from phase I to phase II, 8% of the patients treated with cetirizine, 9% of the patients treated with chlorpheniramine, and 15% of the patients treated with terfenadine used adjunctive beclomethasone. Beclomethasone use was found to have no significant effect on the rankings of the treatment groups. There were no significant differences in the use of pseudoephedrine among treatment groups. There was no significant use of cromolyn sodium during phase II.

Safety

Phase I. Somnolence was reported by 17 of 42 patients receiving chlorpheniramine (40.5%), by five of 43 patients receiving cetirizine (11.6%), and by three of 45 patients receiving terfenadine (6.7%); the differences were significant ($p < 0.01$) for cetirizine versus chlorpheniramine and for terfenadine versus chlorpheniramine. The differences for cetirizine versus terfenadine were not significant. Other frequently reported adverse events were headache (36%), asthenia (7%), and dry mouth (5%); no significant differences were found between treatment groups. No significant changes in laboratory test results were found in any of the treatment groups.

Phase II. Somnolence was reported by only two of 39 patients treated with terfenadine (5.1%), five of 51 patients treated with cetirizine (9.8%), and four of 24 patients treated with chlorpheniramine (16.7%). Headache was reported by 38.6% of all 114 patients and was the most frequently reported adverse event in all treatment groups.

Quality of life

Quality of life was determined by the RQLQ, which captured data on the areas of patients' lives that were affected by rhinoconjunctivitis, such as sleep, symptoms other than SAR, practical considerations, nasal symptoms, eye symptoms, activities, and emotions. The quality of life score for a category was based on the sum of the individual items within that category. The total quality of life score was based on the sum of all categories for each patient.¹²

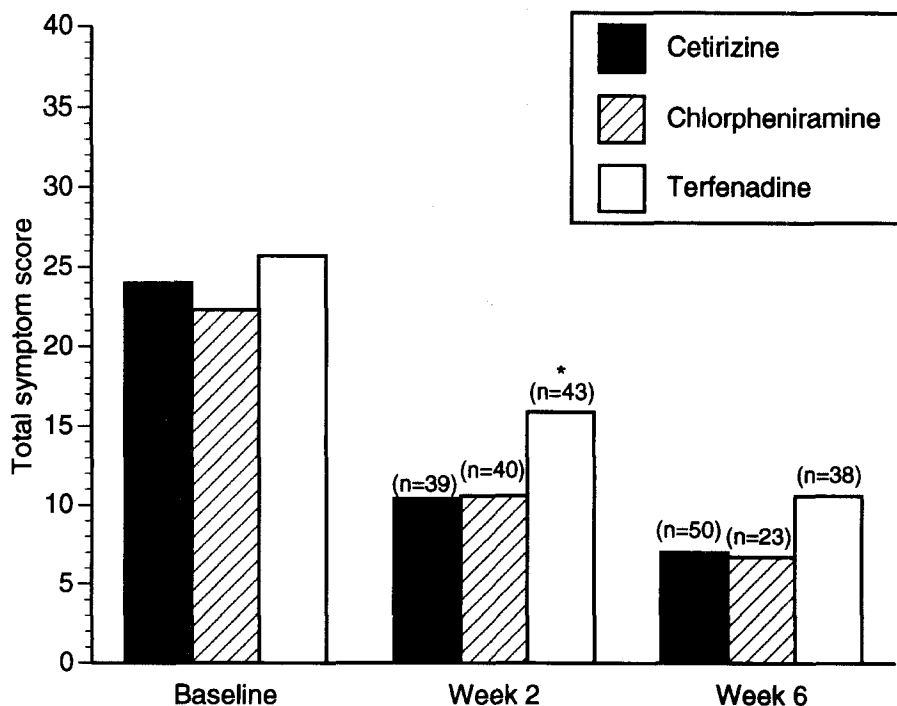


FIG. 1. Mean of patients' evaluations of study drugs. * $p < 0.01$ cetirizine versus terfenadine; $p < 0.05$ chlorpheniramine versus terfenadine.

TABLE III. Patients' evaluations of mean symptom score (± 1 SEM) during phases I and II

Symptom	Phase I			Phase II		
	Cetirizine (n = 39)	Chlorpheniramine (n = 40)	Terfenadine (n = 43)	Cetirizine (n = 50)	Chlorpheniramine (n = 23)	Terfenadine (n = 38)
Sneezing	1.33 $\pm$ 0.25*	1.40 $\pm$ 0.29†	2.74 $\pm$ 0.43	1.00 $\pm$ 0.22	0.87 $\pm$ 0.24	1.61 $\pm$ 0.32
Itchy nose	2.15 $\pm$ 0.32	1.83 $\pm$ 0.27	3.02 $\pm$ 0.40	1.26 $\pm$ 0.22	1.00 $\pm$ 0.27	1.71 $\pm$ 0.31
Nasal congestion	3.13 $\pm$ 0.39	3.45 $\pm$ 0.39	3.72 $\pm$ 0.40	2.68 $\pm$ 0.30	2.00 $\pm$ 0.33	3.45 $\pm$ 0.45
Itchy eyes	1.87 $\pm$ 0.33	1.83 $\pm$ 0.31	2.49 $\pm$ 0.36	1.02 $\pm$ 0.22	1.30 $\pm$ 0.29	1.18 $\pm$ 0.20
Postnasal drip	1.97 $\pm$ 0.40	1.98 $\pm$ 0.32	3.26 $\pm$ 0.44	1.52 $\pm$ 0.29*	1.30 $\pm$ 0.33†	2.74 $\pm$ 0.41
Runny nose	1.67 $\pm$ 0.33*	2.05 $\pm$ 0.35	2.91 $\pm$ 0.42	1.28 $\pm$ 0.25*	1.13 $\pm$ 0.24†	2.21 $\pm$ 0.33
Watery eyes	1.36 $\pm$ 0.27	1.53 $\pm$ 0.28	1.44 $\pm$ 0.29	0.90 $\pm$ 0.20	1.04 $\pm$ 0.34	1.16 $\pm$ 0.21
Total‡	10.36 $\pm$ 1.48*	10.60 $\pm$ 1.33†	15.86 $\pm$ 1.87	6.98 $\pm$ 1.14	6.65 $\pm$ 1.35	10.61 $\pm$ 1.41

* $p < 0.05$ cetirizine versus terfenadine.

† $p < 0.05$ chlorpheniramine versus terfenadine.

‡Total excludes nasal congestion.

Phase I. Significant differences were found between cetirizine and terfenadine in practical considerations, nasal symptoms, and total severity. Differences in impaired activities were noted between the cetirizine and chlorpheniramine groups. At the end of phase I, patients in the cetirizine group had a significantly lower mean total quality of life score than those in the terfenadine and chlorpheniramine groups (the lower the score, the better the quality of life). Mean total symptom RQLQ scores are shown in Fig. 4.

Phase II. At the end of phase II, patients treated with cetirizine had significantly lower mean quality of life scores than patients treated with terfenadine for the total RQLQ, including practical problems, activities, sleep problems, and non-hay fever symptoms (Fig. 4). Patients treated with chlorpheniramine had significantly lower mean quality of life scores than patients treated with terfenadine for sleep problems and non-hay fever symptoms. There were no differences between patients treated with cetirizine and those treated with chlorpheniramine.

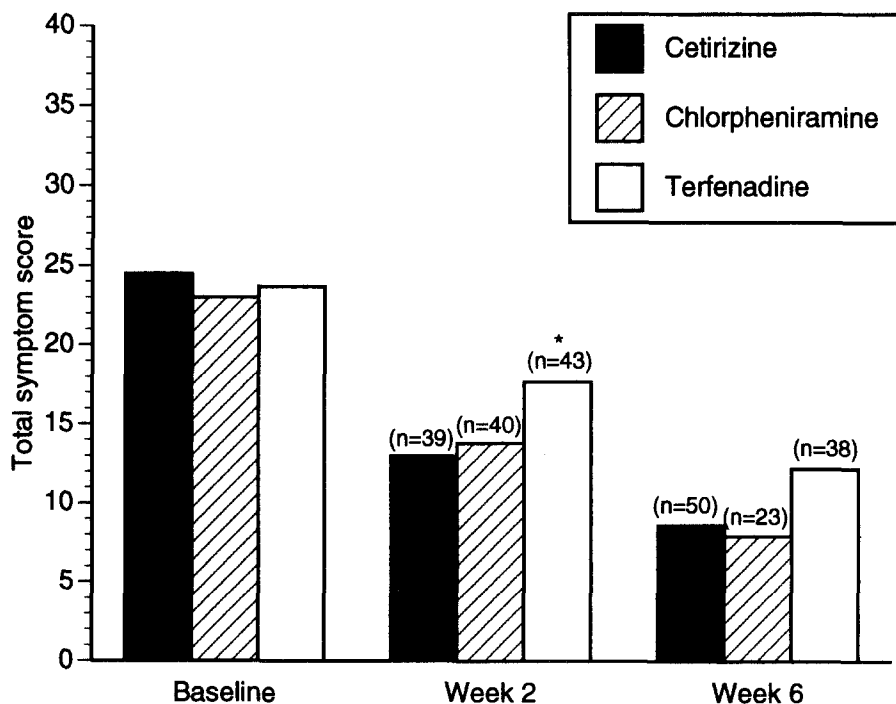


FIG. 2. Mean of physicians' evaluations of study drugs. * $p < 0.01$ cetirizine versus terfenadine; $p < 0.05$ chlorpheniramine versus terfenadine. † $p < 0.01$ cetirizine versus terfenadine and chlorpheniramine versus terfenadine.

Outcome assessment

The MAUT model used in this study evaluated the combination of several outcome variables. Safety consisted of the percentage of patients reporting sedation during phase I. Efficacy consisted of patient and physician total symptom severity scores at the end of phase I and the percentage of patients switching to another treatment at phase II. Patient acceptance consisted of the RQLQ total score at the end of phase I and dose frequency. Cost consisted of only the drug acquisition cost.

Sensitivity analyses were conducted by varying weights and relative drug acquisition costs. Final drug rankings were determined from 300 different valuations on the basis of a pricing range for cetirizine of 1, 1.5, and 2 times that of terfenadine. Overall, cetirizine ranked first 61.3% of the time, chlorpheniramine ranked first 34.3% of the time, and terfenadine ranked first 4.3% of the time. The complete rank percentages are shown in Fig. 5.

DISCUSSION

The results of this trial suggest that cetirizine and chlorpheniramine are comparable to each other and are significantly better than terfenadine in relieving mild SAR symptoms. However, chlor-

pheniramine was associated with significant sedation. At the end of phase I, 28.9% of the patients treated with chlorpheniramine, 50% of the patients treated with terfenadine, and 69.4% of the patients treated with cetirizine were determined to be satisfied with their therapy and were not switched from their medication. This suggests that patients treated with cetirizine were most satisfied with their treatment and that patients treated with chlorpheniramine were least satisfied with their treatment. The switching differences were significant for cetirizine versus chlorpheniramine ($p = 0.001$) and for terfenadine versus chlorpheniramine ($p = 0.05$).

Patients were not blinded to treatment; therefore, it is possible that patient bias may have had some impact on efficacy results. However, the intent of this naturalistic study was to measure the impact on preference of medication in an environment that mimicked clinical practice as closely as possible. To reduce the impact of patient bias, the decision to change medication was a patient and physician consensus made after reviewing patient symptoms and examination at the beginning of phase II. At the end of phase I, patients in the cetirizine group had significantly improved quality of life scores compared with those in the chlorphe-

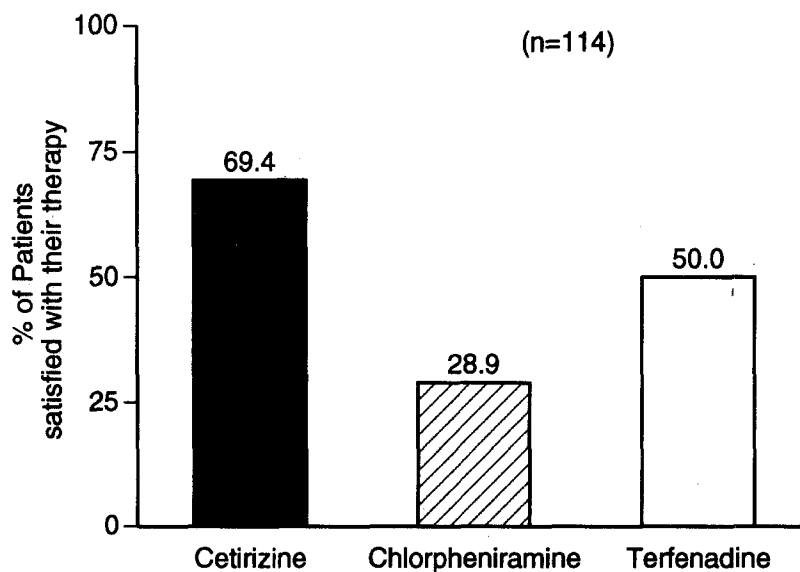


FIG. 3. Comparative patient satisfaction with treatment at the end of phase I.

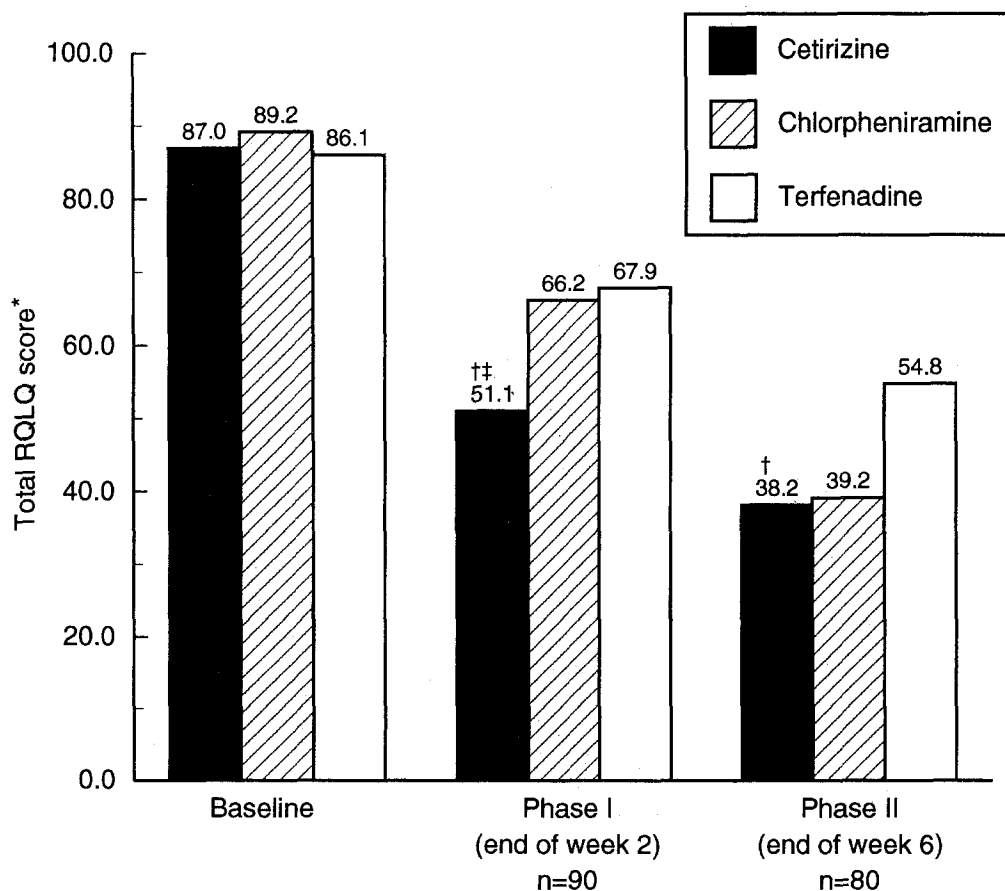


FIG. 4. Mean of the total RQLQ scores for study drugs. *The lower the score, the greater the quality of life. [†] $p < 0.05$ cetirizine versus terfenadine. [‡] $p < 0.05$ cetirizine versus chlorpheniramine.

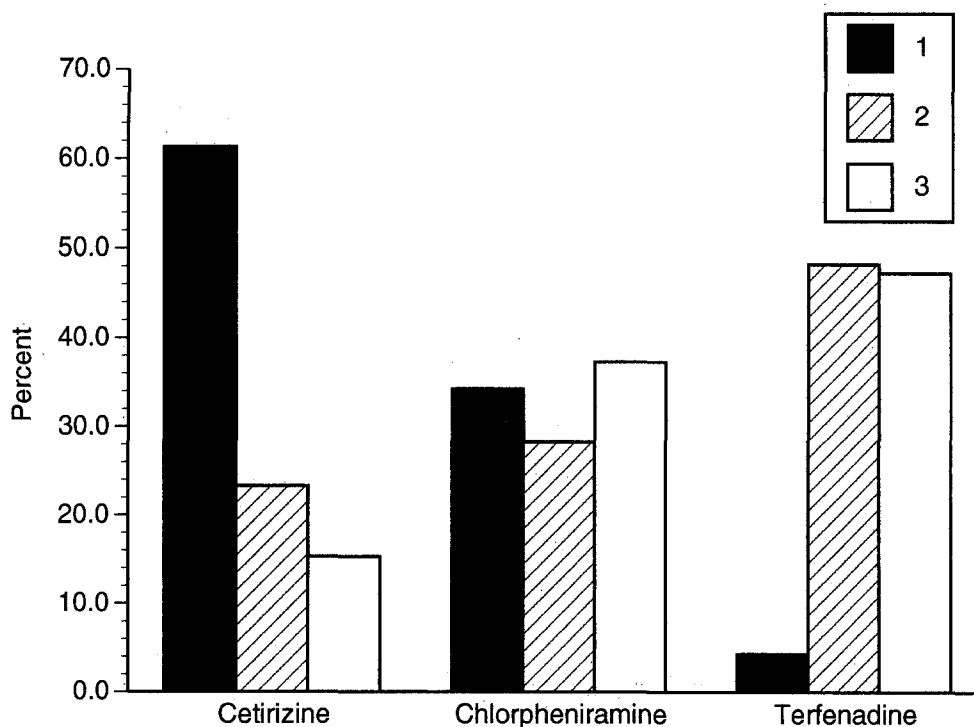


FIG. 5. Rank percentages from the sensitivity analysis. For each combination, the drug with the highest utility score (best performance) is given the rank of 1, the drug with the next highest utility score is given the rank of 2, and the drug with the lowest utility score is given the rank of 3.

niramine and terfenadine groups. At the end of phase II, patients in the terfenadine group had the least improved quality of life score.

Quality of life includes how a patient's physical and emotional functioning are affected by illness or treatment.^{14, 15} Before the development of validated, reproducible instruments sensitive enough to evaluate change in the variables selected to assess physical and emotional functioning,¹⁴ quality of life was difficult to evaluate. Since the development of these instruments,¹⁶ quality of life has gained acceptance as a measure of a therapy's performance.¹⁴ The total quality of life questionnaire is validated, reproducible, and responsive.¹²

RQLQ scores indicated that non-hay fever symptoms often had a severe adverse effect on patients' lives. Headache, which was included among non-hay fever symptoms, was the principal side effect reported by patients in all treatment groups.

The incidence of sedation in this trial was found to be highest with chlorpheniramine and lowest with terfenadine. However, the 40% incidence of sedation reported in phase I for chlorpheniramine was double that usually reported.² Because patients knew which medication they were taking,

they may have anticipated sedation with chlorpheniramine, thereby increasing reports of its occurrence. The 16.7% incidence of sedation reported in phase II more closely reflects the expected incidence of sedation.

According to the limited data collected, organizational costs were minimal. Patients were scheduled to return to the clinic at specified times and were therefore less likely to make additional calls or visits. Data were available for 27 patients in phase I and for 25 patients in phase II. No differences between treatment groups were noted for resource use, which was also limited. Of the direct and indirect patient costs reported, the greatest costs were related to impaired personal time, but few patients (under 20%) recorded cost data in their diaries. More data are needed to help determine the total economic impact of mild SAR on managed health care organizations and on patients.

The MAUT model, which has been used successfully in formulary decision making,¹¹ was used for outcome assessment in this trial. According to our model analyses, which incorporated the selections and weightings of health care staff for efficacy, safety, cost, and patients' quality of life,

cetirizine was ranked most often as the antihistamine of choice, followed by chlorpheniramine and, finally, by terfenadine. When quality of life and sedation are given importance as outcomes, formulary committees are better positioned to make choices for antihistamine acquisition. To reach a reproducible, reliable measure of the value of a medication, multiple outcomes should be used in the formulary decision-making process.

The methodology of this study paralleled the clinical treatment of SAR. In clinical practice, patients may change antihistamines after an initial period or use a second medication for relief of congestion. In the clinical decision-making process, the physician must consider factors relating to a patient's quality of life and learn the extent to which symptoms affect the patient.¹⁷ The RQLQ allowed reproducible scientific assessments of quality-of-life factors, which were used as variables in a multiattribute evaluation. This trial shows that the use of the RQLQ with other measures of efficacy and safety is feasible in clinical studies of SAR and that multiattribute evaluation provides a flexible method for decision making.

This study serves as a model for comparing treatments of SAR and for making formulary decisions. The results of this trial indicate that the selection of an antihistamine for the treatment of SAR is best made by using a multiattribute evaluation that includes quality of life. In this trial cetirizine was the drug favored most often, followed by chlorpheniramine and then terfenadine.

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