

Improvement of quality of life by treatment with cetirizine in patients with perennial allergic rhinitis as determined by a French version of the SF-36 questionnaire

J. Bousquet, MD,^a J. Duchateau, MD,^b J. C. Pignat, MD,^c C. Fayol, PhD,^d P. Marquis, MD,^d S. Mariz, MD,^e J. E. Ware, MD,^f B. Valentin, MSc,^g and B. Burtin, PhD^g Montpellier, France, Bruxelles, Belgium, Lyon, France, Watford, England, Boston, Mass., and Braine-l'Alleud, Belgium

Background and aim: Perennial allergic rhinitis impairs social life, but it is not known whether quality of life may be improved when patients are treated with an H_1 -blocker. A randomized, double-blind, placebo-controlled study was carried out with cetirizine to assess the effect of this drug on quality of life.

Methods: Two hundred seventy-four patients with perennial allergic rhinitis were tested. Quality of life was measured by using the Medical Outcome Study Short-Form Health Survey (SF-36) questionnaire. After a 2-week run-in period, cetirizine, 10 mg once daily, (136 patients) or placebo (138 patients) was given for the next 6 weeks. The SF-36 questionnaire was administered after the run-in period (at the start of treatment) and after 1 and 6 weeks of treatment. Symptom-medication scores were measured daily during the study.

Results: After the run-in period (baseline), there were no significant differences between the cetirizine and placebo groups in terms of symptoms or quality-of-life scores. After 6 weeks of treatment, percentage of days without rhinitis or with only mild rhinitis symptoms was significantly greater in the cetirizine group in comparison with the placebo group ($p < 0.0001$, Mann-Whitney U test). All of the nine quality-of-life dimensions were significantly improved (from $p = 0.01$ to $p < 0.0001$, Mann-Whitney U test) after 1 and 6 weeks of cetirizine treatment compared with placebo. There was no improvement in the placebo group.

Conclusions: This study is the first to demonstrate that an H_1 -blocker, cetirizine, can improve quality of life for patients with perennial allergic rhinitis. (*J Allergy Clin Immunol* 1996;98:309-16.)

Key words: Cetirizine, perennial rhinitis, quality of life, SF-36 questionnaire

Quality of life (QOL) is a concept including a large set of physical and psychologic characteristics assessing the problems in the social context of lifestyle,¹ which may be measured by using general health status or disease-specific scales. The Medical Outcome Study Short-Form Health Survey

Abbreviations used

QOL: Quality of life
SF-36: Medical Outcome Study Short-Form Health Survey

From ^aServices des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, Montpellier; ^bService Immunologie et Transfusion, Hôpital universitaire Saint-Pierre, Bruxelles; ^cHôpital de la Croix-Rousse, Lyon; ^dMAPI, Lyon; ^eUCB Pharma Ltd., Watford, Hertfordshire; ^fNew England Medical Center, Boston; ^gUCB S.A. Pharmaceutical Sector, Braine-l'Alleud.

Received for publication Aug. 16, 1995; revised Dec. 13, 1995; accepted for publication Dec. 21, 1995.

Reprint requests: Jean Bousquet, MD, Services des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, 34295 Montpellier Cedex 5, France.

Copyright © 1996 by Mosby-Year Book, Inc.

0091-6749/96 \$5.00 + 0 1/1/71334

(SF-36) questionnaire is a general health status scale based on 36 questions selected to represent nine health concepts (physical and social functioning, role limitations in physical and emotional problems, mental health, vitality, bodily pain, general perception of health, change of health). It is standardized, widely used, validated,²⁻⁴ and translated into several different languages⁵ and makes it possible to compare healthy subjects and patients.^{6,7}

Perennial allergic rhinitis is a disease causing

variable restrictions on the physical, psychologic, and social aspects of the life of patients, and it may have an impact on their careers. With the SF-36 questionnaire, it has been recently shown that perennial allergic rhinitis induced a severe impairment of QOL⁸ similar to that induced by severe asthma.⁹ QOL was found to be improved by treatment with topical corticosteroids both in seasonal¹⁰ and perennial¹¹ rhinitis. However, because a specific QOL scale was used, it is not known to what extent QOL was improved, and it is not known whether a general QOL scale is sensitive enough to be used during drug trials.

Cetirizine is a potent H₁-receptor blocker,¹² which was found to be effective in the treatment of perennial allergic rhinitis. It was shown to decrease symptoms,¹³ but its effects on QOL had to be demonstrated because there was no published study examining the effects of an H₁-receptor blocker on QOL in rhinitis.

A randomized, double-blind, placebo-controlled, parallel-group study was carried out for 6 weeks in 274 patients with perennial allergic rhinitis to assess the efficacy of treatment with cetirizine, 10 mg once daily, on nasal symptoms and QOL as measured with the SF-36 questionnaire. Outpatients were referred by allergists or ear, nose, and throat doctors in France and ear, nose, and throat doctors in Belgium (list provided in Appendix).

METHODS

Patients

Three hundred thirty-two patients were enrolled in the run-in period, but the study was based on data obtained from 274 patients who were randomized to two treatment groups. They ranged in age from 18 to 60 years and were enrolled between September 1, 1992 and May 15, 1993. All of them had perennial allergic rhinitis characterized by a typical history of perennial rhinitis and an allergy to *Dermatophagoides pteronyssinus* as determined by skin prick tests with standardized allergens (Stallergènes, Fresnes, France or Dome Hollister Stier, Puteaux, France) and/or the presence of serum-specific IgE (RAST or CAP System; Pharmacia Diagnostics, Uppsala, Sweden). A skin test response was considered positive when its size was at least 70% of a positive control (codeine phosphate 9% or histamine dihydrochloride 10 mg/ml). Symptoms had to be present for at least 1 year before patients could be included in the study, and patients had to be receiving continuous treatment.

Patients were excluded if they had taken astemizole or systemic corticosteroids during the 6 weeks before the study. Patients enrolled after February 15 had to be free of pollen allergy, as documented by skin prick test results and/or determination of serum-specific IgE. Because

several parameters may impair QOL, patients were also excluded if they had a known chronic disease that could affect the results of the QOL questionnaire (e.g., asthma, epilepsy, depression, or psychologic disorders), if they were unable to speak French fluently, or if a major event recently occurred (e.g., death of a relative, job loss).

Ethics Committee approvals were obtained in Belgium and France. Written informed consent was given by all eligible patients.

Assessment of the severity of rhinitis

The severity of rhinitis was assessed by means of a diary card. On this card, four rhinitis symptoms (rhinorrhea, obstruction, sneezing, and nasal itching) were recorded once daily by using a 5-point scale, ranging from no symptoms (score 0) to severe, intolerable symptoms (score 4).

QOL questionnaire

The QOL questionnaire used was a French version of the SF-36 questionnaire based on the Medical Outcome Study survey,^{14,15} a standardized, widely used questionnaire, which had been validated in rhinitis.⁸ It is composed of 36 items measuring three major attributes (functional status, well-being, overall evaluation of health), which correspond to nine health concepts. This questionnaire can be completed by most persons in less than 15 minutes. The SF-36 questionnaire can be administered at home and in many other settings; it can be administered by telephone or face-to-face interview or through the mail.¹⁶ The risks of receiving incorrectly filled-in questionnaires and of losing questionnaires are higher when administered at home than when administered in a "face-to-face" clinical setting. However, to avoid the interaction between the respondent and the provider and to diminish as much as possible the influence of the "visit to the investigator" on the respondent's answers, administration at home was preferred. So, patients were instructed to complete on their own, in the home environment, the SF-36 questionnaire they received on visit days and to mail it within 48 hours (preaddressed and stamped envelopes were provided). The scoring system used in the SF-36 questionnaire was performed by the recommended three-step method.¹⁶ The first step involved the re-coding of some items, the second step computed scale scores by summing across items in the same scale, and the third step transformed raw scale scores to a scale of 0 to 100, with a higher score indicating a better health state. The "Reported Health Transition" concept of the SF-36 questionnaire was considered separately (as recommended by the author of the SF-36 questionnaire).

Medications

No treatment for rhinitis (medication or additive allergen avoidance) was allowed during the trial. Because obstruction is a major symptom of perennial rhinitis, the only rescue medication allowed was an

TABLE I. Demographic characteristics at baseline visit

	Cetirizine group (n = 136)	Placebo group (n = 138)	p Value*
Age (yr)			
Median (Q1, Q3)	32.0 (25.0, 43.0)	34.0 (26.0, 44.0)	NS†
Sex			
M (%)	42	50	NS‡
F (%)	58	50	
Marital status			
Single (%)	38	34	NS‡
Married/cohabiting (%)	55	59	
Divorced/separated (%)	6	4	
Widowed (%)	1	3	
Education			
Primary (%)	21	24	NS‡
Secondary (%)	9	7	
A-level (%)	35	35	
Tertiary (%)	2	3	
University (%)	33	31	
Employment			
Full-time (%)	54	57	NS‡
Part-time (%)	11	12	
Retired (%)	5	4	
Unemployed (%)	5	4	
Housewife (%)	7	10	
Student (%)	13	13	
Other (%)	5	0	

Q1, Q3, Quartile 1, quartile 3; NS, not significant.

* Probability to observe such a difference/distribution under the null hypothesis.

† Mann-Whitney U test.

‡ Chi square test.

oxymetazoline nasal spray. This drug was used as required by the patients and quoted on the diary card.

Design of the study

Initial assessment and run-in period. After verification of inclusion-exclusion criteria, demographic data, history of perennial allergic rhinitis, and current and previous treatments for this disease, patients were instructed to discontinue any treatment specific to perennial allergic rhinitis for 2 weeks (medication and/or additive specific measures at home). They were also asked to report on a diary card, each day for 2 weeks, the severity of rhinitis symptoms.

Baseline visit and randomization. Patients were reviewed on day 14 (baseline visit). Diary cards from the run-in period were collected and controlled. Severity was defined as the presence on a diary card of at least 20 of 56 rhinitis scores (14 days $\times$ 4 rhinitis scores per day), quoted as moderately severe or severe (scores ≥ 3). Only patients with severe rhinitis were randomized to cetirizine (10 mg once daily) or placebo groups. The first tablet of medication had to be taken on the day of the baseline visit. Patients randomized to treatment groups received a QOL questionnaire.

Sixty-four investigators participated in the study. De-

pending on their rate of inclusion, the investigators were regularly provided with sets of equal number of drug packages. In each set equilibrium between placebo and cetirizine was respected.

Follow-up. After randomization, patients filled in the diary card daily for the next 6 weeks and were reviewed after 7 days (week 1 visit) and 42 days (week 6 visit). At those two visits, tolerance, compliance with the treatment, concomitant medication use, and significant QOL events were monitored by the investigators. Diary cards were controlled, and QOL questionnaires were given to the patients.

End points

The primary outcome variable was the evolution of the nine health concepts of the SF-36 profile after 1 and 6 weeks of treatment.

Power of the study

On the basis of the results of a previous study,⁸ it was computed that 150 patients per group were needed to detect, with a power of 80% at a 5% significance level, an improvement of at least 30% from baseline values in seven of the nine health concepts of the SF-36 questionnaire in the group treated with cetirizine, whereas no

TABLE II. SF-36 scores: Median (Quartile 1-Quartile 3)

	Baseline	Week 1	Week 6
Physical functioning (PF)			
Cetirizine	87.5 (72.5-97.5)	95.0 (85.0-100.0)	95.0 (90.0-100.0)
Placebo	87.5 (72.5-97.5)	92.5 (75.0-100.0)	90.0 (72.5-97.5)
<i>p</i> Value	NS	NS	0.0007
Role physical (RP)			
Cetirizine	50.0 (25.0-75.0)	100.0 (75.0-100.0)	100.0 (75.0-100.0)
Placebo	50.0 (0.0-75.0)	50.0 (25.0-100.0)	50.0 (25.0-100.0)
<i>p</i> Value	NS	0.0001	0.0001
Bodily pain (BP)			
Cetirizine	62.0 (41.0-100.0)	77.0 (62.0-100.0)	84.0 (74.0-100.0)
Placebo	62.0 (41.0-92.0)	64.0 (41.0-84.0)	62.0 (51.0-100.0)
<i>p</i> Value	NS	0.0001	0.0001
General health (GH)			
Cetirizine	47.0 (32.0-62.0)	57.0 (47.0-72.0)	67.0 (52.0-77.0)
Placebo	52.0 (35.0-67.0)	52.0 (35.0-72.0)	52.0 (37.0-67.0)
<i>p</i> Value	NS	NS	0.0001
Vitality (VT)			
Cetirizine	50.0 (40.0-65.0)	65.0 (50.0-75.0)	70.0 (55.0-80.0)
Placebo	50.0 (40.0-65.0)	50.0 (40.0-70.0)	50.0 (33.3-70.0)
<i>p</i> Value	NS	0.0001	0.0001
Social functioning (SF)			
Cetirizine	62.5 (50.0-75.0)	75.0 (62.5-100.0)	87.5 (75.0-100.0)
Placebo	62.6 (50.0-75.0)	75.0 (50.0-87.5)	62.5 (37.5-87.5)
<i>p</i> Value	NS	0.0014*	0.0001
Role emotional (RE)			
Cetirizine	66.67 (33.33-100.0)	100.0 (66.67-100.0)	100.0 (100.0-100.0)
Placebo	66.67 (33.33-100.0)	66.67 (33.33-100.0)	66.67 (33.33-100.0)
<i>p</i> Value	NS	0.0014	0.0001
Mental health (MH)			
Cetirizine	60.0 (44.0-76.0)	68.0 (60.0-80.0)	76.0 (64.0-88.0)
Placebo	60.0 (52.0-72.0)	60.0 (52.0-76.0)	60.0 (48.0-72.0)
<i>p</i> Value	NS	0.0015	0.0001

Probability (*p*) values were determined by Mann-Whitney U test.

NS, Not significant.

* Identical medians but statistically different average ranks.

improvement was expected in the group treated with placebo.

Statistical analysis

QOL data and clinical efficacy data were analyzed on an intention-to-treat basis,¹⁷ so all patients randomized to treatment groups were included in the analysis. The Last Value Carried Forward method was used to handle the problem of missing values.

All tests were two-tailed and performed at the 5% level of significance. When multiple comparisons occurred, a conservative Bonferroni's correction was applied. Group comparability was accepted for *p* values above 0.05.

The demographic characteristics of the patients were analyzed by using the Mann-Whitney U test to compare age in both groups and by using the chi-square test to compare distributions of sex, marital status, education,

and employment. Severity of rhinitis at the baseline visit was analyzed by means of the Mann-Whitney U test.

Clinical efficacy measured on diary cards was evaluated as the percentage of days (between baseline and week 6 visits) with no symptom scored above 1 (no or only mild symptoms) when all symptoms were considered together. These percentages were computed in each group and compared by using the Mann-Whitney U test. Percentages of days with use of rescue medication (between baseline and week 6 visits) were also analyzed in the same way.

SF-36 profiles at baseline, week 1, and week 6 visits were compared in both groups: each concept of the SF-36 questionnaire was analyzed separately by using the Mann-Whitney U test. The "Reported Health Transition" concept in both groups was analyzed by using the Mantel-Haenszel chi-square statistic. Improvement of each concept of the SF-36 questionnaire (week 1 - baseline

TABLE III. Reported Health Transition (HT)

	Much worse		Somewhat worse		About the same		Somewhat better		Much better		p Value
	n	%	n	%	n	%	n	%	n	%	
Baseline											
Cetirizine	13	10.74	35	28.93	57	47.11	14	11.57	2	1.65	NS
Placebo	14	11.29	22	17.74	66	53.23	17	13.71	5	4.03	
Week 1											
Cetirizine	1	0.85	9	7.63	31	26.27	48	40.68	29	24.58	<0.001
Placebo	3	2.56	15	12.82	65	55.56	29	24.79	5	4.27	
Week 6											
Cetirizine	1	0.91	6	5.45	44	40.00	39	35.45	20	18.18	<0.001
Placebo	9	8.11	14	12.61	63	56.76	17	15.32	8	7.21	

Probability (*p*) values were determined by Mantel Haenszel statistics.

NS, Not significant.

visits; week 6 – baseline visits) in both groups was analyzed with the same methods.

Data management and statistics were performed on an 80486 CPU 50 MHz IBM-compatible computer with SAS software (version 6.08 for MS-Windows) under license from SAS Institute Inc. (Cary, N.C.).

RESULTS

Recruitment, demographic characteristics, and group comparability

Among the 274 patients randomized to treatment groups at the baseline visit, 136 received cetirizine, and 138 received placebo. The two groups were matched in terms of demographic characteristics (Table I). Severity of rhinitis at baseline visit was comparable in both groups: the median (first and third quartiles) number of nasal scores of 3 or greater, observed during run-in period, was 29 (21.5, 37.5) for cetirizine and 29 (24.0, 37.0) for placebo (*p* = NS, Mann-Whitney U test).

Of the patients randomized to treatment groups, 249 (90.9%) returned the QOL questionnaire that they received at the baseline visit (126 in the cetirizine group and 123 in the placebo group). Baseline scores for the nine health concepts were comparable (Tables II and III).

Lost to follow-up, protocol deviations, and compliance

Ten (3.6%) patients (5 in the cetirizine group and 5 in the placebo group) were lost to follow-up between baseline and week 1 visits, and another patient (placebo group) was lost to follow-up between week 1 and week 6 visits.

In 16 (5.8%) patients (9 in the cetirizine group

and 7 in the placebo group), at least one protocol deviation was reported (use of forbidden medications, incorrect compliance, modification of daily life, or early cessation because of inefficacy). At the end of the study, 248 patients were assessed, 122 (89.7%) in the cetirizine group and 126 (91.3%) in the placebo group.

Clinical efficacy of the treatment and rescue medications

For an ideal number of 42 days, the number of days correctly filled in on the diary cards was 40.6 ± 6.5 days (mean $\pm$ SD) in the cetirizine group and 40.7 ± 6.1 days in the placebo group. Between baseline and week 6 visits, the percentage of days with no or only mild rhinitis symptoms (all symptoms considered) was significantly greater in the cetirizine group than in the placebo group (median [first and third quartiles]: cetirizine, 42.5% [4.7%, 68.3%]; placebo, 2.6% [0.0%, 28.6%]; *p* < 0.0001; Mann-Whitney U test).

Patients receiving cetirizine used significantly less rescue medication than patients receiving placebo (*p* = 0.0009, Mann-Whitney U test). The median percentage of days with use of rescue medication was 11.9% (first and third quartiles: 0.0%, 51.1%) in the cetirizine group and 32.5% (first and third quartiles: 4.8%, 85.7%) in the placebo group.

Efficacy as determined from SF-36 questionnaire

Among the 274 patients randomized to treatment groups, 240 (87.6%) and 227 (82.8%) returned their SF-36 questionnaires after week 1 and week 6 visits. Among these questionnaires, 227

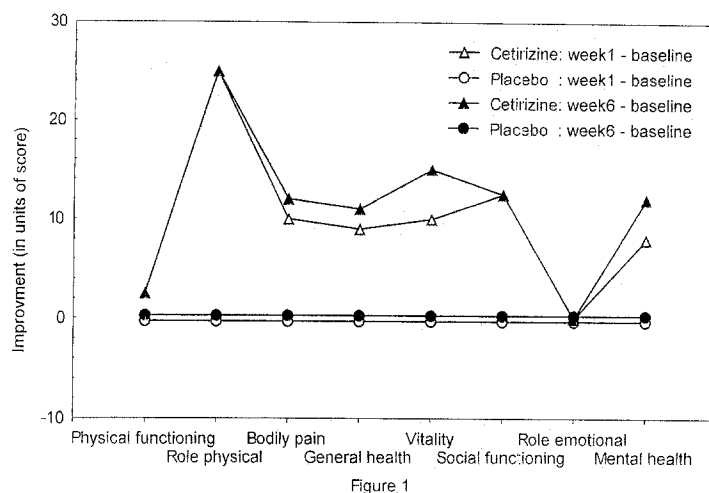


FIG. 1. Median improvements (in units of score) between baseline and visits at weeks 1 and 6.

(94.6%) and 210 (92.5%) were filled in completely (no missing data). Mean percentage ($\pm$ SD) of missing data was 0.21% (1.25%) for questionnaires at week 1 visit and 0.40% (3.6%) for questionnaires at week 6 visit. These results show the questionnaire's good acceptability.

SF-36 scores at week 1 and week 6 visits are presented in Tables II and III. Almost all scores at both visits were significantly higher during cetirizine administration than during placebo administration.

Median improvements (week 1 – baseline visits), (week 6 – baseline visits) of all the SF-36 scores except "Reported Health Transition" are presented in Fig. 1. After 1 week of treatment, all QOL scores of patients receiving cetirizine, compared with those receiving placebo, had already improved significantly ("Role Emotional": $p = 0.01$; "Physical Functioning": $p = 0.005$; all other scores: $p < 0.0001$; Mann-Whitney U test). This improvement was more pronounced after 6 weeks of treatment.

Adverse events

Among the 274 patients randomized to treatment groups, 41 (15%) (21 in the cetirizine group and 20 in the placebo group) reported adverse events. Sixteen patients receiving cetirizine and 14 receiving placebo reported a single adverse event, five patients receiving cetirizine and four receiving placebo reported two adverse events, and two patients receiving placebo reported three and five adverse events, respectively. There was no significant difference in the severity, nature, and fre-

quency of the reported adverse events between the two groups.

DISCUSSION

In this study cetirizine, an H_1 -blocker, was found to reduce daily symptoms and improve QOL by comparison with placebo. Moreover, it was observed that there was no placebo effect in the evaluation of QOL.

QOL scales can be divided into general scales, making it possible to compare patients with any disease with healthy subjects and disease-specific scales, which are more adapted to clinical trials. Although it is important to assess precisely the evolution of QOL by using scores adapted to a specific disease during clinical trials, it may be equally important to determine whether a therapeutic intervention may improve QOL in such a way that the patient may recover a normal social life. The SF-36 QOL score is widely used throughout the world and is already validated for healthy subjects and a variety of chronic diseases. We decided to use the SF-36 questionnaire for the following reasons: (1) the questionnaire was translated into French, and the validation of the translation had been assessed⁵; (2) it is simple and easy to use and can be completed in about 10 minutes; (3) it can be self-administered; (4) its reliability has been validated^{19, 20}; and (5) we had already shown that patients with perennial allergic rhinitis demonstrated an impairment of QOL scores when compared with normal subjects. However, it was not known whether a treatment might improve QOL scores when a general scale is used in perennial allergic rhinitis.

In this study the efficacy of cetirizine was confirmed in perennial allergic rhinitis: daily symptoms were significantly reduced in the cetirizine group. Moreover, use of rescue medications was lower in this group as compared with the placebo group. This study confirms results of a previous double-blind, placebo-controlled study in perennial allergic rhinitis.¹³ Moreover, it must be noted that improvement already observed after 1 week of treatment was significantly more important at the end of the treatment period, suggesting that long-term treatment is needed to further reduce symptoms of perennial allergic rhinitis.

It has been shown that specific scales of QOL can be used to monitor the treatment of allergic rhinitis,^{10, 11} and it has been found that QOL scores can be improved by treatment. However, it was not known whether a general scale of QOL might be sensitive to changes during a drug trial. The results of this study show that the SF-36 questionnaire is a sensitive measure of QOL, which was found to be significantly improved within a week of treatment. All QOL scores were improved by cetirizine treatment. Perennial allergic rhinitis was found to severely impair QOL, and it is important to show that a treatment for allergic rhinitis not only decreases symptoms but can also improve QOL. However, only a general QOL scale can demonstrate to what extent social life is improved. These results show that for most QOL scores, cetirizine administration improves QOL to a level that does not make it possible to differentiate control subjects examined during a previous study⁸ and treated patients. Such a result should be confirmed but highlights the importance of using sensitive general QOL scales, such as the SF-36 questionnaire.

It would also be interesting to verify in other studies whether the SF-36 questionnaire is sufficiently responsive to detect differences not only between active treatments and placebo but also between two or more active treatments.

In other respects, to verify that the evolution of QOL scores observed in this study reflects change in Health Related Quality of Life, additional analyses were planned and are ongoing. The aims of these analyses are to determine the association between the evolution of clinical symptoms (diary scores by the patient and investigators' scores) and the evolution of QOL scores. Preliminary results show that, as expected, a positive association appears between evolutions of clinical symptoms and QOL scores. This association is stronger for the

symptoms recorded on the diary cards than for symptoms scored by the investigators.

Similarly, other studies need to be performed to investigate the possible specific correspondence between some rhinitis symptoms and some QOL dimensions.

For both the symptom and QOL scores, a statistically significant difference between treatments does not necessarily indicate something in real life. It appears that improvement in mental health scores may not be clinically relevant for the patients. On the other hand, the improvement in most of the scores is likely to be clinically relevant.

In this study, patients receiving placebo did not show any improvement in QOL scores, suggesting that QOL reflects closely the improvement of the patients and is a measure of their overall satisfaction during a treatment. On the other hand, these patients demonstrated a decrease in symptoms called the *placebo effect*, a characteristic of most if not all trials examining the effects of antiallergic drugs in rhinitis. This placebo effect, not observed on QOL, may be of importance in future studies to confirm that QOL scores are not influenced by placebo in order to propose QOL as a measure of efficacy in clinical trials.

REFERENCES

1. Walker SR, Rosser RM. Quality of Life: assessment and application. Ciba Found Symp 1987;169-78.
2. Stewart AL, Hays RD, Ware JE Jr. The MOS Short-Form General Health Survey. Reliability and validity in a patient population. Med Care 1988;26:724-35.
3. Stewart AL, Ware JE, editors. Measuring functioning and well-being. The Medical Outcomes Study approach. Durham, NC: Duke University Press, 1992.
4. McHorney CA. The validity and relative precision of MOS, short- and long-form health status scales and Dartmouth Coop Charts. Med Care 1992;30(5 Suppl):253-65.
5. Aaronson NK, Acquadro C, Alonso J, et al. International quality of life assessment (IQOLA) project. Qual Life Res 1992;1:349-51.
6. Tarlov AP, Ware JE Jr, Greenfield S, Nelson EC, Perrin E, Zubkoff M. The Medical Outcomes Study: an application of methods for monitoring the results of medical care. JAMA 1989;262:925-30.
7. Stewart AL, Greenfield S, Hays RD, et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes study. JAMA 1989; 262:907-13.
8. Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. J Allergy Clin Immunol 1994;94:182-8.
9. Bousquet J, Knani J, Dhivert H, et al. Quality-of-Life in

- asthma. I. Reliability and validity of the SF-36 Questionnaire. *Am J Respir Crit Care Med* 1994;149:371-5.
10. Juniper EF, Guyatt GH, Archer B, Ferrie PJ. Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: further exploration of "as needed" use. *J Allergy Clin Immunol* 1993;92:66-72.
 11. Juniper EF, Guyatt GH, Anderson B, Ferrie PJ. Comparison of power and aerosolized budesonide in perennial rhinitis: validation of rhinitis quality of life questionnaire. *Ann Allergy* 1993;70:225-30.
 12. Rihoux JP, Dupont P. Comparative study of the peripheral and central effects of terfenadine and cetirizine 2 HCl. *Ann Allergy* 1987;59:235-8.
 13. Mansmann HC, Altman RA, Berman BA. Efficacy and safety of cetirizine therapy in perennial allergic rhinitis. *Ann Allergy* 1992;68:348-53.
 14. Ware JE, Sherbourne CD. The MOS 36-item Short-Form health Survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
 15. McHorney CA, Ware JE, Raczeck AE. The MOS-36-item Short-Form Health Survey (SF-36). II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247-63.
 16. Ware JE. SF-36 Health Survey. Manual and interpretation guide. Boston: Nimrod Press, 1993.
 17. Biostatistical methodology in clinical trials applications for marketing authorizations for medicinal products. European Community, Note for guidance, III/3630/92 final, 1994.
 18. Brazier JE, Harper R, Jones NMB, et al. Validating the SF-36 Health Survey Questionnaire: new outcome measure for primary care. *Br Med J* 1992;305:160-4.
 19. Jenkinson C, Coulter A, Wright L. The Short Form 36 (SF-36) Health Survey Questionnaire: normative data for adults of working age. *Br Med J* 1993;306:1437-40.
 20. Brooks CD, Karl KJ, Francom SF. Profile of ragweed hay fever symptom control with terfenadine started before or after symptoms are established. *Clin Exp Allergy* 1990;20:21-6.

APPENDIX

Allergists - France (ALLERGOLOGUES - FRANCE)

Arfi, Thierry (Nice)
 Azas, Patricia (Marseille)
 Banoun, Laurence (Le Raincy)
 Barnier, Jean-Charles (Nantes)
 Benjelloun, Badia (Paris)
 Bensa, Alain (Nice)
 Berkou, Nora (Paris)
 Bettendorf, Alain (Nice)
 Bidet, Béatrice (Fontenay sur Bois)
 Boyer, Guy (Nice)
 Courtois Delair, Lysiane (Suresne)
 Dallara, Jean Marie (Strasbourg)
 Decor, Yves (Montpellier)
 Delsaux, Marie-Christine (Gournay sur Marne)
 Diancourt, Jean-Marie (Strasbourg)
 Dittli, Brigitte (Avignon)
 Dubreil, Yannick (Nantes)
 Dupont, Patricia (Saint-Cloud)
 Durand Perdriel, François (Nantes)
 Girodet, Bruno (Bron)
 Grange, François (Lyon)
 Ickovic, Marie Roger (Montreuil)
 Ilassan, Ghatfan (Plessis Trevis)
 Langlois, Luc (Nantes)
 Laurent, Philippe (Marseille)
 Lefrancois, Jocelyne (Montpellier)
 Louis, Stéphane (Nice)
 Mangiapan, Luc (Tourcoing)
 Marache, Evelyne (Villeneuve D'ascq)
 Martinat, Yan (Lyon)
 Massardier, Gille (Nice)
 Megret, Danielle (Meyzieu)
 Merland, Nathalie (Montpellier)
 Nedjat Bakhch, Aligholi (Paris)
 Pigearias, Bernard (Nice)

Puech, Nicole (Lunel)
 Rouimi Navarro, Ruth (Nice)
 Saal, Bernard (Paris)
 Sebban, Michel (Marseille)
 Serca Tassy, Véronique (Nantes)
 Signoret, Robert (Marseille)
 Tobalem, Véronique (Villeurbanne)
 Verdier, Geneviève (Montpellier)
 Vetillard, Roger (Toulouse)
 Vialette, Roland et Fargeon, Jean-Paul (Marseille)
 Wurmser, Patrice (Villeneuve Saint-georges)

ENT - France

Alabert, Jean-Pierre (Montpellier)
 Beaudot, Jean Dominique (Lyon)
 Boachon, Georges (Lyon)
 Camuzard, Jean François (Nice)
 Coze, Jean François (Lyon)
 Dubreuil, Christian (Pierre Benite)
 Giraud, Roger (Lyon)
 Maligot, Christian (Oullins)
 Palleri, Jean-Claude (Nice)
 Piffaut, Anne-Marie (Lyon)
 Valenza, Jean-Jacques (Nantes)

ENT - Belgique

Brouwez, Michel (Bruxelles)
 Deleuze, Michel (Meslin Eveque)
 Garnir, Jean Jacques (Gembloux)
 Gasmanne, Paul (Charleroi)
 Kennes, Bernard (Montigny Le Tilleul)
 Maisin, Jean-Pierre (Bruxelles)
 Nyst, Marc (Gozée)