



# Levocetirizine improves health-related quality of life and health status in persistent allergic rhinitis<sup>☆</sup>

G. Walter Canonica<sup>a,\*</sup>, Jean Bousquet<sup>b</sup>, Geneviève Van Hammée<sup>c</sup>,  
Claus Bachert<sup>d</sup>, Stephen R. Durham<sup>e</sup>, Ludger Klimek<sup>f</sup>, Joaquim Mullol<sup>g</sup>,  
Paul B. Van Cauwenberge<sup>d</sup>, the XPERT study group

<sup>a</sup>Allergy & Respiratory Diseases Clinic, DIMI, Genoa University, Pad. Maragliano, L.go R. Benzi 10, 16132 Genoa, Italy

<sup>b</sup>Service des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, 34295 Montpellier Cedex 5, France

<sup>c</sup>UCB S.A. Global Health Outcomes Research, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium

<sup>d</sup>Department of Oto-Rhino-Laryngology, Ghent University Hospital, De Pintelaan 185, B-9000, Ghent, Belgium

<sup>e</sup>National Heart and Lung Institute, Royal Brompton Hospital, Imperial College School of Medicine, Dovehouse Street, London, SW3 6LY, UK

<sup>f</sup>Center for Allergy and Rhinology, An den Quellen 10, D-65183 Wiesbaden, Germany

<sup>g</sup>Unitat de Rinologia Servei de Otorinolaringologia, Hospital Clínic c/ Villarroel, 170 08036 Barcelona, Spain

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## KEYWORDS

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## Summary

**Background:** Allergic rhinitis is a chronic respiratory disorder with a detrimental impact on health-related quality of life (HRQOL) and health status. Enhancement and maintenance of patient function and well-being are therefore considered as essential.

**Objective:** To determine whether long-term treatment with levocetirizine 5 mg improves HRQOL and health status in persistent allergic rhinitis (PER) patients assessed with RQLQ and SF-36 scales over a 6-month period.

**Methods:** The Xyzal<sup>®</sup> in PER Trial (XPERT<sup>™</sup>) was a multi-center, double-blind, parallel-group study. A total of 551 patients were randomized to receive levocetirizine 5 mg or placebo once daily for 6 months and assessed for symptoms, HRQOL (Rhinoconjunctivitis Quality of Life Questionnaire: RQLQ) and health status (SF-36). Sensitivity of the RQLQ and SF-36 to disease severity was tested to ensure

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\*Corresponding author. Tel: +39 010 3538931/+39 010 3538933; fax: +39 010 3538904.

E-mail address: [canonica@unige.it](mailto:canonica@unige.it) (G. Walter Canonica).

their suitability for use in PER patients. Treatment effect was assessed by means of repeated measures analyses.

**Results:** Over the 6-month treatment period, levocetirizine showed statistically significant improvements over placebo in HRQOL ( $P < 0.001$  for all RQLQ domains and overall scores) and health status ( $P \leq 0.004$  for SF-36 physical and mental summary scores;  $P < 0.05$  for all SF-36 scales). The relative improvement of levocetirizine over placebo exceeded the predefined clinically meaningful threshold of 30% for all RQLQ scores and the improvement from baseline was 3 times the established MID for RQLQ.

**Conclusion:** The RQLQ and SF-36 could be used to measure HRQOL and health status in PER patients. Long-term treatment with levocetirizine provides sustained improvement of HRQOL and reduces disease burden in PER patients.

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## Introduction

Allergic rhinitis (AR) is a common chronic respiratory disease affecting 10–40% of the population worldwide.<sup>1,2</sup> Its prevalence has been increasing regularly for many years, doubling within 10 years.<sup>3</sup> AR is a disease of bothersome symptoms, such as rhinorrhea, sneezing, nasal congestion, itching of the nose and/or conjunctivitis and is often associated with comorbid disorders including asthma, chronic sinusitis, otitis media, and lower respiratory tract infection.<sup>4</sup> The management of allergic rhinitis involves reducing the causes (allergen avoidance, immunotherapy) and controlling the manifest symptoms (pharmacotherapy).<sup>5,6</sup> The first-line treatment for the control of symptoms is administration of H<sub>1</sub>-receptor antagonists.<sup>7</sup>

AR may significantly impair patient's health-related quality of life (HRQOL), a component of overall quality of life that reflects the impact of disease and treatment on patient's physical and emotional functioning and well-being.<sup>8–10</sup> It has been recognized as an essential outcome measure that complements clinical assessments to support treatment decisions.<sup>11,12</sup> Since AR can adversely affect daily activities, sleep patterns, mental and social functioning, work and school-related performance, which consequently result in substantial social and economic costs,<sup>13–15</sup> the enhancement and maintenance of patients' HRQOL are considered as essential in the treatment of AR.

AR was traditionally classified as seasonal (SAR) and perennial (PAR) allergic rhinitis based on time of exposure. This classification, however, did not entirely correspond to the patients' pattern of AR symptoms as patients with perennial symptoms quite often also have seasonal exacerbations and additionally, not all patients with PAR have symptoms present during the whole year.<sup>16</sup> To meet these concerns, the World Health Organization Initiative on Allergic Rhinitis and its Impact on

Asthma (ARIA, 2001) suggested a new classification of AR as "intermittent" (IAR) or "persistent" (PER) based on the frequency and duration of symptoms.<sup>17</sup> Persistent corresponds to symptoms present for more than 4 days a week and for more than 4 weeks, suggesting the presence of chronic inflammation whereas intermittent corresponds to symptoms present less than 4 days a week or for less than 4 weeks. This classification has been recently validated.<sup>18,19</sup>

Until recently, the effect of an H<sub>1</sub>-antihistamine on HRQOL and health status was not studied in AR patients diagnosed according to the newly defined ARIA classification. The Xyzal<sup>®</sup> in Persistent Rhinitis Trial (XPRT<sup>™</sup>) was the first large study investigating the effects of a modern H<sub>1</sub>-antihistamine in the treatment of PER, as defined by ARIA, over a 6-month period.<sup>20</sup> The study compared the impact of levocetirizine 5 mg, a potent new-generation antihistamine, and placebo on efficacy, safety, HRQOL (measured using the Rhinoconjunctivitis Quality of Life Questionnaire: RQLQ) and health status (measured using the Medical Outcomes Survey Short Form 36: SF-36). This study showed that treatment with levocetirizine led to significant symptom relief and provided a fast and sustained improvement of the HRQOL and health status in patients with PER. However, since the primary aim of the XPRT study was to evaluate the effect of treatment on symptoms and HRQOL after 4 weeks' treatment, the individual RQLQ domains and the SF-36 scales were not presented over the entire study period.<sup>20</sup>

An important aspect of assessments that are repeated over time, however, is that they may be dependent on each other. It has been suggested that repeated assessments over time should be subjected to analysis using a longitudinal modeling approach.<sup>21</sup> Furthermore, when questionnaires are used for the first time in a newly defined patient population, the sensitivity of the questionnaires in

detecting differences between patients with different levels of disease severity should be tested.<sup>21</sup> Consequently, the main objectives of this exploratory study were to determine how improvements in HRQOL and health status noted in PER patients treated with levocetirizine 5 mg daily were translated into the RQLQ domains and SF-36 scales and to address the time issue for analysis of HRQOL and health status in the XPERT study, by comparing the treatment effects on the RQLQ and SF-36 scores over the 6-month period as a whole. Additionally, the sensitivity of the RQLQ and SF-36 to the disease severity of PER patients was addressed.

## Materials and methods

XPERT was a multinational, double-blind, randomized study comparing the impact on HRQOL, efficacy and safety of levocetirizine 5 mg versus placebo administered once daily over a 6-month period in PER. At an initial visit, patients were included in the study if they reported PER symptoms (i.e., rhinitis lasting 4 days or more per week for 4 consecutive weeks or more per year) and were sensitized to both house dust mites and pollen. At the randomization visit 1 week later, patients were enrolled provided their Total 5 Symptoms Score (i.e., sneezing, rhinorrhea, itchy nose, itchy eyes and nasal congestion) evaluated over the selection week was  $\geq 6$  (max = 15) for at least 4 days. During the treatment period, patients attended five visits, 1 and 4 weeks, 3, 4.5 and 6 months after the randomization visit. Authorized rescue medications were nasal or ocular cromoglycate after 1 week of treatment, and prednisolone (20 mg/day for 5 days twice during the study) after 4 weeks. Symptoms, HRQOL and health status were recorded by the patients using an electronic diary (Minidoc<sup>®</sup>, Arracel, Sittingbourne, UK). The electronic mode of administration of HRQOL questionnaires has shown advantages in terms of accuracy and quality of data collection, compared to the paper version.<sup>22–24</sup>

The study protocol was approved by independent ethics committees and all participants signed an informed consent form prior to study entry.

### Health-related quality of life assessment

HRQOL was assessed by means of the self-administered version of the RQLQ.<sup>25</sup> The questionnaire was completed at the beginning of the randomization visit and at each visit during the treatment period or at the end of study treatment in case of

withdrawal. The RQLQ is a disease-specific, validated instrument for evaluating HRQOL on the basis of how symptoms and treatment affect patient's physical, social and emotional well-being. It comprises 28 items combined in 7 domains (activity limitations, emotional function, eye symptoms, non-hayfever symptoms, nasal symptoms, practical problems and sleep problems). Patients were asked to recall their experiences during the previous week and to give their responses on 7-point scales ranging from 0 (i.e. not troubled/none of the time) to 6 (i.e. extremely troubled/all the time). Results were expressed as the mean score of all the items (overall RQLQ score) and the mean score of the items within each domain (domain score). A high score indicates a poor quality of life.

### Health status assessment

Health status was assessed using the self-administered SF-36. The questionnaire was completed at the beginning of the randomization visit and at each visit during the treatment period except after 1 week or at the end of study treatment in case of withdrawal. The SF-36 is a generic questionnaire that has been validated and widely used. It is composed of 35 items measuring 8 health concepts (or scales), and 1 reported health transition item. The 8 health concepts (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) are summarized in two components, one physical (PCS) and one mental (MCS). Patients were asked to recall their experience during the month preceding the visit and to mark their responses using ordinal scales or "yes/no" formats. Scoring of SF-36 items and scales was carried out according to the instructions described in the SF-36 Health Survey Manual.<sup>26</sup> Scale scores range from 0 to 100, with 100 indicating the most favorable health status. The aggregated PCS and MCS scores are standardized to have a mean of 50 and a standard deviation of 10.<sup>27</sup>

### Symptom severity assessments

Each evening, patients were asked to score symptoms of PER (sneezing, rhinorrhea, itchy nose, itchy eyes and nasal congestion) occurring in the last 24 h on a 4-point scale: 0 = absent; 1 = mild; 2 = moderate and 3 = severe. The sum of each of the 5 symptoms, i.e. T5SS, was used to assess the PER severity and subsequently the sensitivity of the RQLQ and SF-36 questionnaires to disease severity

of PER patients. Scores ranged between 0 (no symptoms) and 15 (most severe symptoms).

**Statistical analysis**

A total sample size of 500 patients was planned to detect a treatment difference of 0.36 in the change from baseline of the RQLQ overall score after 4 weeks with a power of 87%, an overall alpha error of 5% and a standard deviation of 1.3. This difference corresponded to a 40% improvement over placebo, assuming an improvement from baseline for placebo of 0.9. All analyses were performed on the intention-to-treat population (ITT). Last Observation Carried Forward method was applied in order to replace missing HRQOL and health status data.

The sensitivity of the questionnaires to PER severity was assessed by means of analyses of variance comparing the scores at baseline (i.e. randomization visit) across four severity groups created on the basis of the 25th, 50th and 75th percentiles of the mean T5SS between selection and randomization visits. The global treatment effect over the 6-month period was estimated from repeated measures analyses on the change in scores from baseline with treatment, country and visit (time effect) as factors, treatment by visit interaction, and baseline scores as covariate.

A 30% relative difference over placebo in the change from baseline of the RQLQ overall score was predefined as clinically meaningful prior to patient enrolment by the study advisory board members. This threshold was also used to interpret the results for the RQLQ domain scores. All statistical tests were two-sided and conducted at the 0.05 significance level.

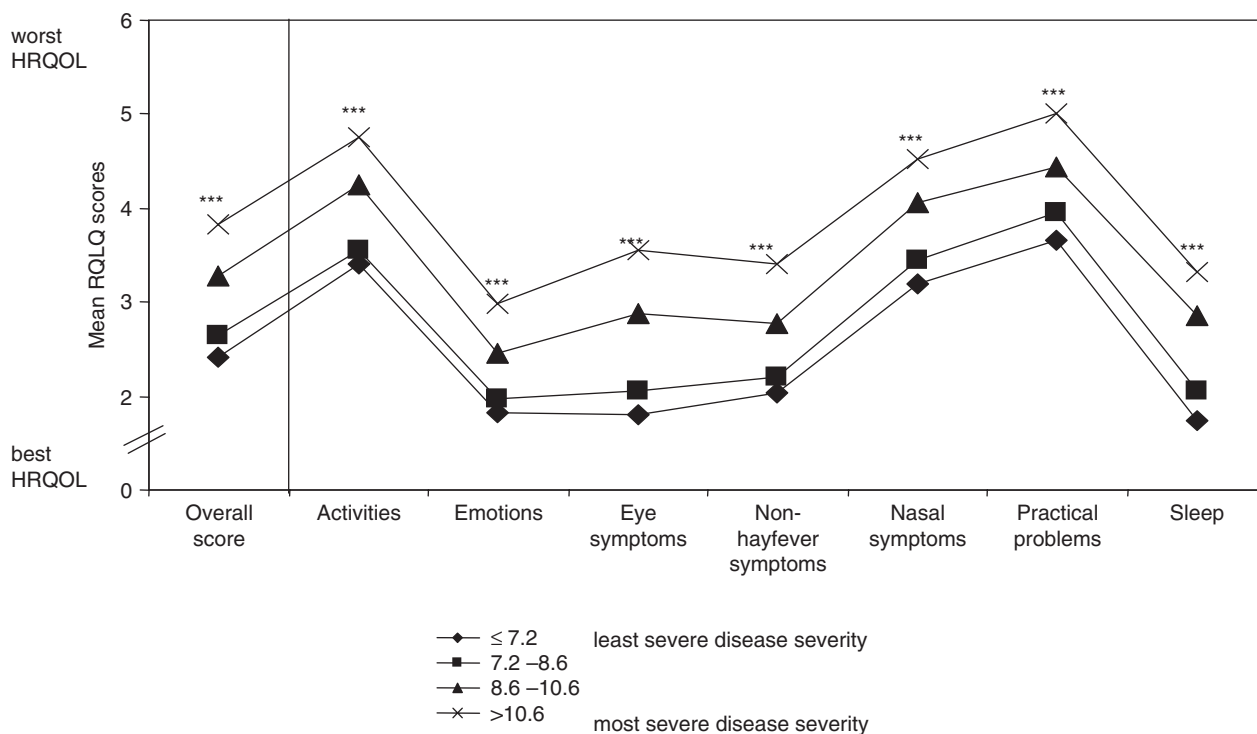
**Results**

**Baseline characteristics**

Data for the two treatment groups (273 patients in the placebo group and 278 in the levocetirizine group) and patient demographics for these groups have been reported in greater detail elsewhere (20). Both groups were comparable at baseline with regard to HRQOL and health status.

**RQLQ and SF-36 scores according to PER severity**

Baseline mean RQLQ domain and overall scores and mean SF-36 PCS, MCS and scale scores are presented by PER severity level in Figs. 1 and 2 respectively. The degree of impairment in both the HRQOL and health status was generally related to



**Figure 1**

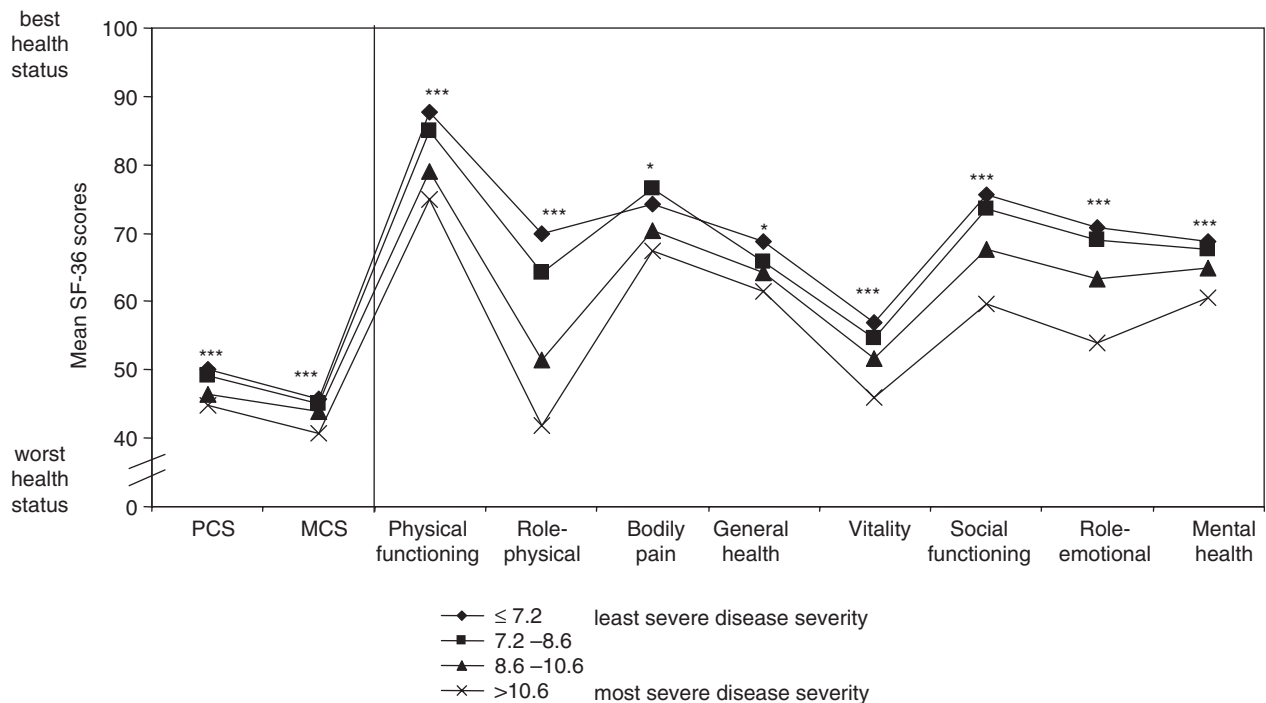


Figure 2

the severity of disease, defined using the T5SS over the week before baseline. While patients with greatest T5SS (most severe disease) showed the greatest impairments in their RQLQ and SF-36 scores, the patients with lowest T5SS (least severe disease) showed lowest impairments. The only exception to this finding was noted for the SF-36 score for bodily pain, which was found to be highest for the patient group with the second least severe disease severity level (Fig. 2).

Comparison of the mean overall and individual domain scores of the RQLQ for the different severities showed that these were all significantly different between the four severity groups (all  $P < 0.001$ ) (Fig. 1). Similarly, comparison of the overall physical and mental component summary scores and individual scale scores of the SF-36 showed that these were all significantly different between the different severity groups (all  $P < 0.001$ , except for the SF-36 bodily pain and general health scales:  $P < 0.05$ ) (Fig. 2).

Additionally, analyses of the RQLQ individual domain scores showed that activities, practical problems, nasal symptoms, and to a lesser extent eye symptoms domains were the most impaired, as compared to the other RQLQ domains, across all disease severity levels (Fig. 1). For the SF-36, the role-physical, vitality, and role-emotional scale scores were the most impaired across all disease severity levels when comparing SF-36 scores to each other (Fig. 2).

### Global treatment effect over the 6-month treatment period

Adjusted mean changes from baseline over the 6-month treatment period are presented in Fig. 3 for the RQLQ overall and domain scores and in Fig. 4 for the SF-36 component summary and scales scores. Levocetirizine led to significantly greater improvements than placebo over the entire treatment period for all scores of both questionnaires (RQLQ: all  $P < 0.001$  for the domain and overall scores; SF-36:  $P < 0.001$  for PCS,  $P = 0.004$  for MCS, all  $P < 0.05$  for the scales).

The relative improvement for levocetirizine over placebo for the whole treatment period was 36.4% for the RQLQ overall score and ranged from 31.3% to 40.8% for the RQLQ domain scores, of which improvements for activities (38.5%), emotions (37.4%), eye symptoms (40.2%), nasal symptoms (40.3%), and sleep (40.8%) were of similar magnitude. Since all the RQLQ domain and overall scores exceeded the predefined threshold of 30% for clinical significance, the improvements in HRQLQ overall and individual domain scores noted for levocetirizine were deemed to be clinically relevant. With respect to the SF-36 scores, the differences in mean changes in scores between treatment groups were shown to be particularly large for the role-physical and role-emotional scales (placebo minus levocetirizine:  $-9.92$  and  $-7.16$ , respectively).

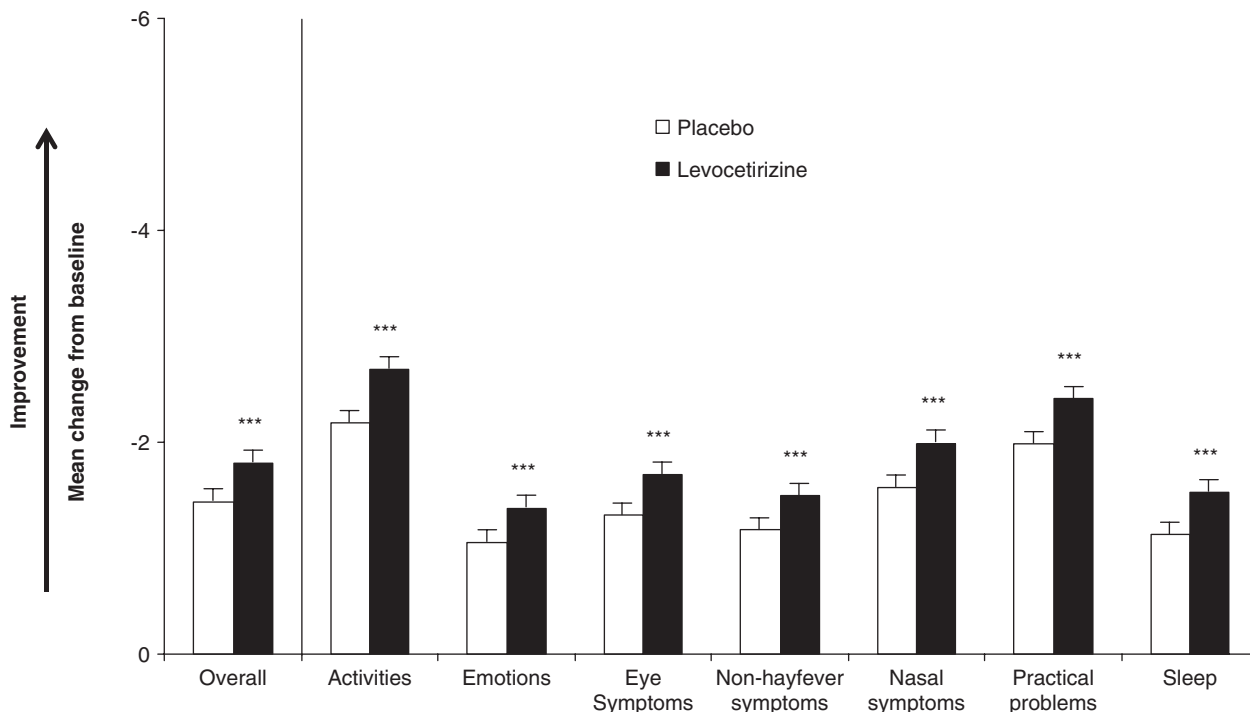


Figure 3

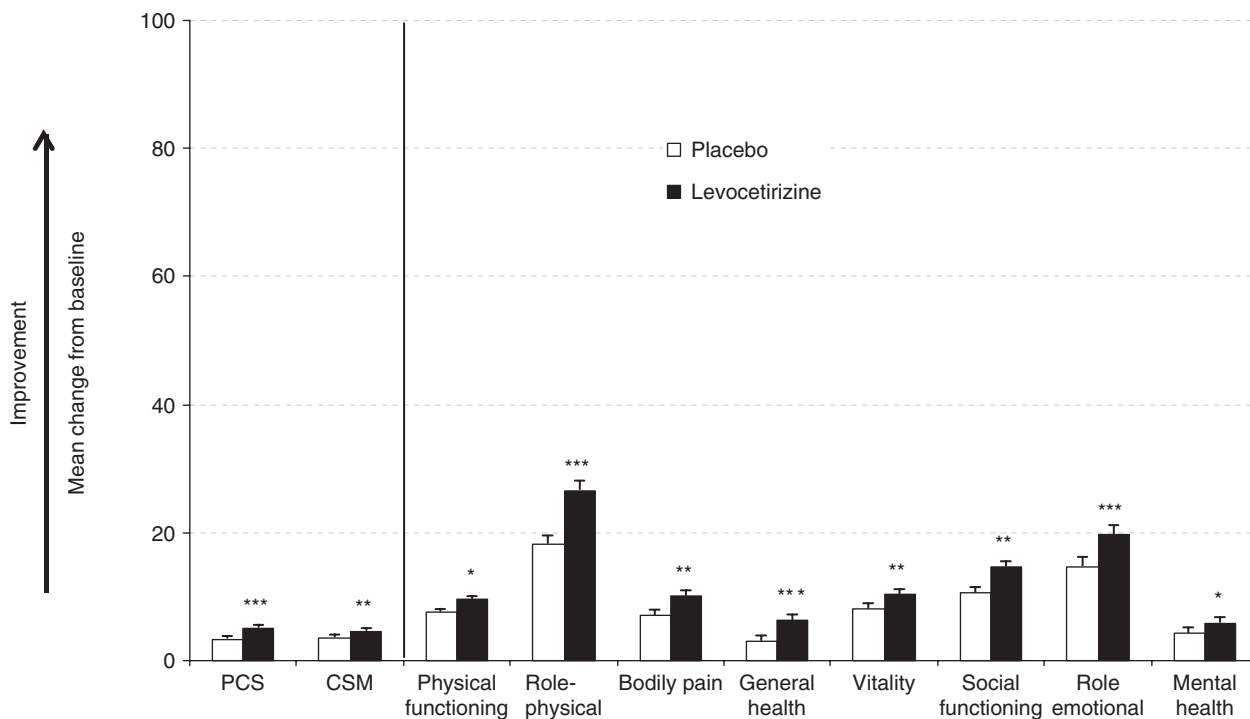


Figure 4

With one exception, the time effect was also statistically significant for all scores (RQLQ: all  $P < 0.001$  for the domain and overall scores; SF-36:  $P < 0.001$  for PCS and MCS, all  $P < 0.05$  for the scales

except general health), indicating that mean changes in scores from baseline were more pronounced over time. No statistically significant treatment by time interaction was found for any



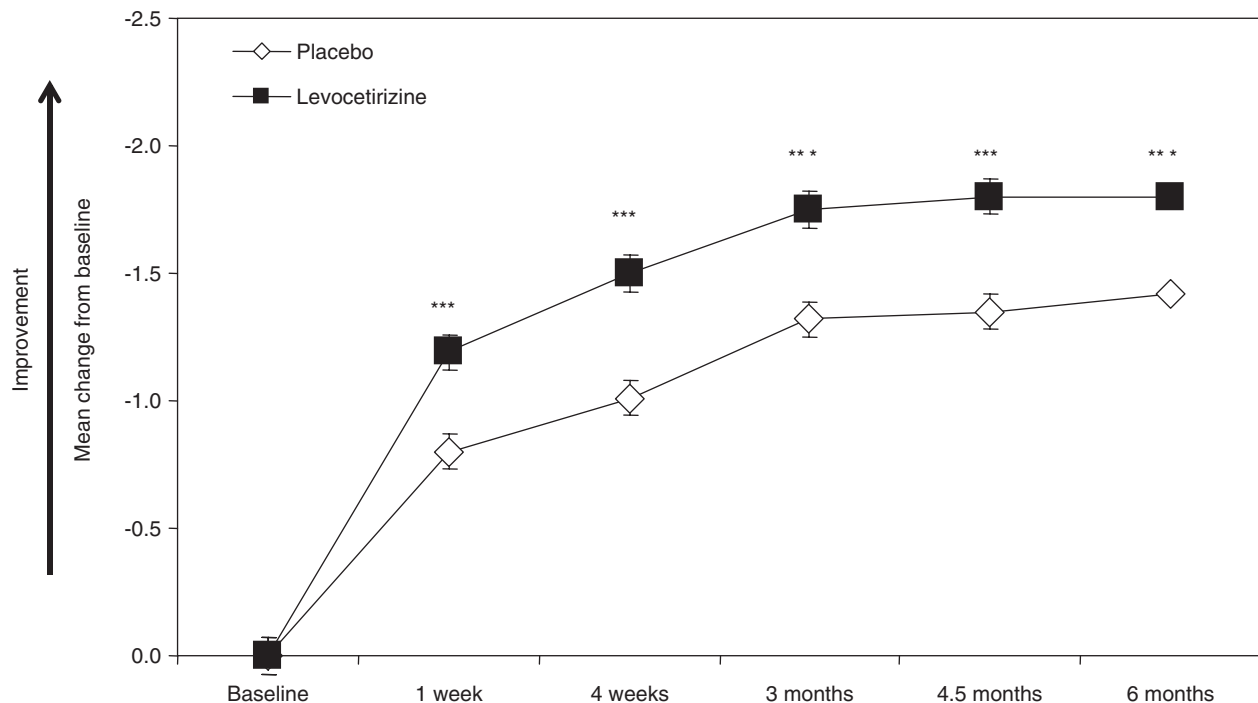


Figure 5

RQLQ or SF-36 score, showing that differences in mean changes in scores from baseline between treatment groups were similar over time, with higher improvements noted for levocetirizine at all visits. Figure 5 illustrates these results for the RQLQ overall score.

## Discussion

It is now recognized that management of allergic rhinitis should be aimed at reducing impairments considered important by the patient, including those associated with comorbid disorders.<sup>15,28</sup> It has also been advocated that the intensity of HRQOL deterioration should first be taken into account rather than severity of AR symptoms to determine the level of treatment.<sup>29</sup> Regarding PER, symptoms are, by definition, chronic and have been shown to have a huge impact on the HRQOL and health status of house dust mite sensitive rhinitis subjects with symptoms for most of the year.<sup>30</sup> More recently, XPERT was the first study to investigate the long-term treatment effect of an antihistamine, levocetirizine 5 mg, on HRQOL and health status in PER patients, as defined by the ARIA guidelines.<sup>20</sup> The HRQOL and health status were assessed by means of the RQLQ<sup>25</sup> and the SF-36,<sup>26</sup> two well-validated and widely used questionnaires considered as complementary to provide

a multi-perspective view of illness burden.<sup>9</sup> Treatment with levocetirizine 5 mg once daily significantly improved the RQLQ overall score from week 1 to 6 months, compared with placebo. Similarly, levocetirizine also significantly improved the SF-36 physical component summary scores from weeks 4 to 6 months and the mental component summary scores after 3 months and 4.5 months of treatment, compared with placebo.<sup>20</sup> The levocetirizine-mediated improvements in HRQOL and health status of PER patients is of particular relevance, because a comparison of the extent of HRQOL impairment experienced by house dust mite-sensitized PER subjects and controls has indicated that the PER patients were significantly more distressed than controls in the RQLQ nose and eye symptoms domains as well as in the non-hayfever domain for all seasons during the year.<sup>30</sup> Additionally, PER patients were also characterized by significantly lower scores in the SF-36 general health and vitality scales in autumn and in the role-physical and role-emotional scales in the other seasons. Similarly, comparisons of the XPERT baseline SF-36 scale scores with the norms of the general US population has shown that the burden of PER was marked, being the largest for the role-physical, the role-emotional and the social functioning scales.<sup>31</sup>

The present study builds on the XPERT study. The findings from this study clearly demonstrate that the overall degree of impairment in both the

HRQOL and health status of PER patients was related to the severity of disease, defined according to the T5SS noted for these patients during the week before baseline. Furthermore, this study showed that activities, practical problems, nasal symptoms and eye symptoms domains of the RQLQ, and role-physical, vitality, and role-emotional scales of the SF-36 were most impaired across all disease severity levels in PER. Assessment of the treatment effects using the RQLQ and SF-36 in the XPERT study showed that levocetirizine led to statistically significant larger improvements of HRQOL and health status than placebo over the whole treatment duration in PER. This was true for all RQLQ domains and the overall score, despite substantial improvements in the placebo group, as well as for all SF-36 scales and the two summary measures. Furthermore, the greater improvement observed in the levocetirizine group was apparent as early as after 1 week and was sustained at each visit until 6 months, as indicated by the absence of interaction between time and treatment effects. This confirms the results observed when comparing the effect of levocetirizine and placebo on the aggregated RQLQ and SF-36 scores at each visit separately<sup>20</sup> and indicates that the beneficial impact of levocetirizine on PER was extended to each aspect of HRQOL and health status investigated either by the disease-specific or the generic instrument. Indeed, since the improvements for levocetirizine were significantly greater than for placebo, these findings collectively suggest that, apart from the prevalent bothersome nasal and eye symptoms of allergic rhinitis, the inability to perform general/physical activities and the presence of practical problems, in particular, may additionally contribute to both the impairment in HRQOL/health status of PER patients and the effect of any treatment in these patients.

Although this study has not compared HRQOL and health status of PER patients versus those of control subjects, our findings are nevertheless in accordance with the findings of others, particularly with respect to the individual RQLQ domains and SF-36 scales most affected. In a recent study, Downie and colleagues<sup>30</sup> showed that house dust mite-sensitive PER patients were significantly more troubled by nasal and eye symptoms, reduced productivity and feeling of being worn out and tired, compared with controls. Similarly, the SF-36 scores for role-physical, role-emotional, vitality, and general health components were significantly lower in PER patients than in control subjects. Other studies employing the SF-36 for assessing the health status in subjects with intermittent and persistent rhinitis<sup>32</sup> and persistent rhinitis<sup>33</sup> have also shown that

role-physical, role-emotional, vitality, and general health components are particularly affected. Comparison of results from these later studies<sup>32,33</sup> and our study, however, warrants caution because these studies were performed in SAR/PAR patients classified as "intermittent" and "persistent" rhinitis prior to the introduction of the specific ARIA classification, especially since IAR and PER are not analogous with SAR and PAR, respectively.<sup>18,19</sup> Nevertheless, the substantial placebo effect on RQLQ scores noted in our study has also been shown to be in line with symptomatic improvements reported by others in placebo-treated allergic rhinitis patients.<sup>34,35</sup>

Although the RQLQ and SF-36 have been widely used for assessing the impact of disease and treatment on quality of life in patients suffering from PAR and SAR,<sup>15</sup> there is a marked paucity of similar data in PER patients as defined by the ARIA criteria. While the sensitivity of these questionnaires in detecting differences in HRQOL and health status of this patient group needs to be confirmed in several large studies, the findings from the present study that the RQLQ domain and overall scores and the SF-36 summary measures and scales were sensitive to disease severity suggests that these instruments are suitable for assessing treatment effects in patients with PER.

In the present study, a 30% relative difference in the change from baseline of the RQLQ overall score for active versus placebo treatment was predefined as clinically meaningful by the study advisory board members based on their clinical experience and knowledge of the disease and the patients. This clinically relevant difference was exceeded with levocetirizine treatment reaching a relative improvement over placebo for the whole treatment period of 36.4%. Moreover, a minimal important difference (MID, i.e., the smallest difference in score which a patient perceives as being beneficial) of 0.5 in the change in RQLQ score from baseline has also been used to determine the clinical relevance of RQLQ score changes as a result of treatment.<sup>36</sup> Our data suggest that levocetirizine achieves 3 times the MID (an RQLQ score of 1.49 versus baseline) which is a confirmation of the clinical relevance of our findings. Even versus placebo, the difference was almost one MID (0.48) which on the one hand is a confirmation of the high standards set by the study board members and on the other it suggests that MID of the same magnitude (0.5), however, versus placebo (not versus baseline as per original research) is also plausible and should be further evaluated.

Despite the strong evidence for positive treatment effects of levocetirizine on HRQOL and health



status in PER patients, this study is not without some limitations. Foremost, patients were allowed to use limited amounts of nasal or ocular cromoglycate and in worst cases oral prednisone as rescue medication, which could attribute to differences in outcomes between the two treatment groups. While this is feasible, it is more likely that the effects of rescue medication were probably biased in favor of improvements in placebo-treated patients, who were shown to be using more rescue medication over the entire 6-month study period than levocetirizine-treated patients.<sup>20</sup> Indeed, this being the case it is possible that greater rescue medication use by this group of patients may have contributed to the substantial placebo effect noted in this study, although this remains to be substantiated in another controlled trial.

In conclusion, this study expands the findings of the XPERT study and provides valuable insights into the therapeutic management of HRQOL and health status in PER patients. Results indicated that the degree of impairment in both the HRQOL and health status of PER patients was related to the disease severity and that long-term treatment with levocetirizine 5 mg was effective in providing clinically meaningful and sustained improvement of HRQOL and to reduce the burden of disease through improvement of health status. This is in keeping with other studies which have also demonstrated that the effects of long-term regular daily administration of an H<sub>1</sub>-antihistamine did not wane and were beneficial in treatment of AR and/or its comorbid diseases.<sup>37,38</sup> We could confirm that RQLQ is a very sensitive disease-specific instrument. The generic SF-36 instrument showed a lower sensitivity, although certain of its scales (e.g. role-physical, role-emotional and general health) were more sensitive than others.

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