

ORIGINAL PAPER

Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and inflammatory parameters

M. Pasquali, I. Baiardini, A. Rogkakou, A.M. Riccio, C. Gamalero, D. Descalzi, C. Folli, G. Passalacqua and G.W. Canonica

Allergy and Respiratory Diseases, DIMI, University of Genoa, Genoa, Italy

Clinical and Experimental Allergy

Summary

Background Levocetirizine (LCZ) has been shown to be effective in allergic rhinitis. We evaluated its clinical efficacy, antiinflammatory actions and its effects on quality of life (QoL) with a specific instrument in the asthma–rhinitis comorbidity.

Methods Fifty adult patients with persistent rhinitis with/without asthma were enrolled. After a 1-week run-in for baseline evaluation, they were randomized to LCZ or placebo for 8 weeks. Cromolyn and salbutamol were permitted on demand. Rhinoconjunctivitis and asthma symptoms were evaluated by diary cards. QoL was assessed by the specific Rhinasthma questionnaire and the generic SF-36 at different time-points. Nasal scrapings and lavages were also performed for inflammatory cell count and mediator assessment.

Results Ten patients dropped out for unrelated reasons and the remaining completed the study with no side-effect. Symptoms began to decrease in the active group at the second week of treatment when the difference with the placebo group became significant (0.05) and so remained until the end of the trial. Starting from 2 weeks of therapy, there was a significant decrease vs. baseline in all the four components of the Rhinasthma questionnaire only in the active group. The intergroup comparison became significant ($P < 0.05$) at 4 weeks. The SF-36 detected only sporadic differences between groups. Eosinophils and neutrophils in nasal scraping were significantly decreased in the LCZ group vs. baseline at all times. Nasal mediators were under the detection limits and no analysis could be performed. In the active group, only two patients used rescue medications compared with 13 patients in the placebo group.

Conclusions LCZ is clinically effective and capable of improving the rhinitis–asthma-related QoL.

Keywords allergic rhinitis, asthma, levocetirizine, quality of life

Submitted 14 March 2006; revised 8 May 2006; accepted 9 June 2006

Correspondence:

Prof. G. Walter Canonica, Allergy and Respiratory Diseases, DIMI, Pad.

Maragliano, Lgo R. Benzi 10, 16132

Genoa, Italy.

E-mail: canonica@unige.it

Introduction

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa, initiated by an IgE-mediated reaction that follows the exposure to allergens [1]. It is characterized by typical clinical symptoms (itching, rhinorrhoea, sneezing and congestion), associated or not with conjunctivitis, which can be intermittent or persistent, as established in the more recent guidelines [2]. Of note, persistent AR is often associated with comorbid asthma [3] and is a significant risk factor for asthma development [4]. This fact results in substantial costs [5] and measurable effects on the well-being and productivity of patients [6, 7]. Thus, it has become clear that in evaluating the effectiveness of

a treatment for AR, not only symptoms should be taken into account but also quality of life (QoL). This should be done by using both generic and disease-specific instruments. Moreover, in AR, a complex inflammatory process also takes place, where numerous mediators, receptors and cells inflammatory are involved [8]. This is the reason why nasal corticosteroids are highly effective, although the more recent antihistamines have been shown to display some additional antiinflammatory actions that are advantageous in the management of AR [9].

Antihistamines are one of the first-line drugs recommended in every step of severity of AR, due to their very favourable risk-to-benefit ratio [2, 9]. Among the latest generation antihistamines, levocetirizine (LCZ) [10] has

been shown to be effective in relieving symptoms of seasonal and perennial rhinitis [11, 12] and in improving the QoL of rhinitis patients [13]. LCZ possesses a very favourable pharmacokinetics and pharmacodynamic profile with high selectivity for the H1 receptor, low volume of distribution and virtually no liver metabolism [10, 14] or drug-to-drug interaction. Owing to the favourable characteristics and to the encouraging results obtained in previous trials, we attempted to evaluate the clinical effects of LCZ in AR with concomitant asthma, with particular attention to the changes in QoL. This was done by means of a recently developed instrument that takes into account not only the rhinitis aspects but also the impact on QoL of lower airways symptoms [15] and the combined effect of the upper and lower respiratory diseases. We evaluated, as secondary outcomes, the possible effects of the drugs on inflammatory cells and mediators in the nose.

Methods

Overall design

The study was designed as a double-blind, placebo-controlled, randomized, two parallel arm trial. Patients with persistent AR and asthma, after a 1-week run-in period, were randomized to receive daily either placebo or LCZ 5 mg for 8 weeks. Total symptom scores, rescue medications and tolerability were recorded throughout the 9 weeks. QoL (generic and specific) and nasal inflammatory cells and mediators were assessed at the end of run-in (visit 2), after 2 (visit 3), 4 (visit 4) and 8 weeks (visit 5) of treatment. The specific questionnaire was also recorded at enrolment (visit 1). The study design is outlined in Fig. 1.

The study was approved by the inner Ethical Committee and conducted according to the Good Clinical Practice rules. All patients gave their written informed consent before enrolment.

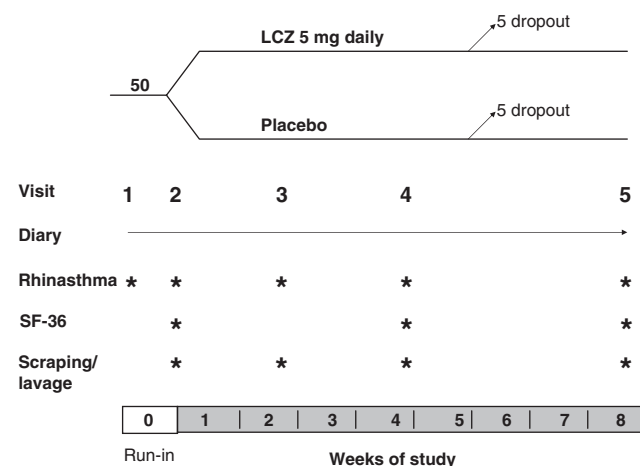


Fig. 1. Study design.

Patients

Adult outpatients (>18 years) of both genders having persistent allergic rhinoconjunctivitis with a history of mild intermittent asthma from at least 2 years or actual asthma (last month) were enrolled. The diagnosis of persistent rhinitis was made on a clinical basis, according to the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria [2], whereas asthma was diagnosed and graded according to GINA guidelines [16]. A positive (weal diameter >3 mm) skin prick test (SPT) and/or CAP-RAST (class II or higher) for at least house dust mites and/or parietaria was required. The SPTs were performed with a standard panel of allergens common in our region, including the following: dust mites, grasses, parietaria, birch, alder, olive, cypress, cat, dog, *Alternaria* and *Aspergillus*.

Exclusion criteria were as follows: anatomical abnormalities of the nose (turbinate hypertrophy, septal deviation, polyps), pregnancy, persistent asthma, chronic treatment with systemic steroids, malignancies, systemic immunological disorders and ongoing specific immunotherapy.

Study drug and concomitant medications

After completing the 1-week run in, patients were randomly assigned to receive either LCZ 5 mg or placebo daily. Treatment codes were assigned on the basis of a computer-generated random sequence. Active drug and placebo in tablets were undistinguishable in aspect, size and flavour. At visit 2, after randomization, patients were provided with the package of blinded drug and rescue medications. All patients were allowed to use, as rescue medications on demand, cromolyn nasal spray and/or cromolyn eye drops (two to four times daily) and inhaled salbutamol. No other medication for asthma, rhinitis or conjunctivitis was allowed during the study.

Quality of life assessment

The impact of illness and therapy was assessed by the specific Rhinasthma [15] questionnaire. Rhinasthma consists of 30 items and for each of them patients have to indicate on a Likert scale (1 = not at all; 5 = very much) how much they were troubled by each problem. This questionnaire takes into account the functional, physical and emotional problems experienced by adult patients with respiratory allergy, and provides three separate scores for upper airways, lower airways, respiratory allergy impact. Moreover, the Rhinasthma provides a composite score, namely the Global Summary, which computes the aggregate scores and indicates the overall impact of the disease. All the four scores are from 0 to 100, where a higher score indicates worst QoL. The Rhinasthma

questionnaire evaluates the QoL in the previous 2 weeks. A generic QoL questionnaire, the SF-36 [17], was also used to evaluate the health status of patients, assessing the overall QoL independent of the symptoms. The SF-36 explores the past 4 weeks and is composed of 36 items corresponding to eight domains: physical function, role limitation (physical), bodily pain, general health, vitality, social function, role limitation (emotional) and mental health. A higher score indicates a better health status on a 0–100 scale.

Clinical diary

Throughout the study (including the run-in week), patients had to fill a diary card for symptoms. All symptoms were graded using a score from 0 (absent at all) to 3 (very troublesome). Five symptoms were considered for rhinoconjunctivitis (so-called T5SS): rhinorrhoea, itching, sneezing, nasal congestion and ocular itching. Also, five lower airways symptoms (cough, wheezing, dyspnoea, chest tightness, night awakenings) had to be recorded. Moreover, patients had to record on the same diary card how many times he/she used nasal and ocular cromones and/or salbutamol. A weekly symptom score (possible maximum value 105) was calculated for statistical analysis.

Inflammatory parameters

A rhinoprobe device was used to scrape the mucosa of the inferior turbinate. After scraping, it was immersed into 2 mL phosphate-buffered saline and transferred to a polypropylene tube for cytopspin (150 µL of fluid; 750 g for 3 min). Specimens were then spread on glass slides, air dried, stained with May–Grunwald Giemsa and examined by light microscopy (Olympus U-SPT; Olympus, Italia, Rome, Italy) [18]. The number of eosinophils and neutrophils was expressed as percentage of the total cells, with 400 cells counted per specimen.

To assess intracellular adhesion molecule-1 (ICAM-1) expression [18], slides prepared as above were rehydrated with PBS for 10 min and assayed with an immunoperoxidase staining. Samples were incubated for 30 min with an appropriate dilution of ICAM-1 antibody, rinsed in PBS pH 7.6 and incubated for 20 min with the Envision system. The positive reaction was detected with DAB. Negative controls incubated without the primary antibody were also used. Positive epithelial cells were expressed as percentage of total epithelial cells on each slide.

Nasal lavage fluids were obtained after nasal scraping according to an established method [19]. Five milliliter of normal saline, pre-warmed to 35 °C, was instilled into each nostril and held for 10 s using the Valsalva manoeuvre. The fluid expelled after asking the subject to blow the nose gently was collected into a funnel connected to a

30 mL container. Lavages were centrifuged at 1100g for 10 min and the supernatants were harvested and stored at –20 °C. ECP and tryptase in nasal lavage fluids were performed with the FEIA technique (UNICAP Pharmacia, Uppsala, Sweden).

Statistics

Descriptive analysis was carried out for the demographic characteristics, and a comparative analysis between groups was performed by the χ^2 test. Comparative inter-group and intra-group analyses were performed using a two-tailed *t*-test for unpaired and paired samples, respectively. *P* values of 0.05 or less were considered significant. The study was sized assuming with α 0.01 a power of 90% to detect a change of 15% in T5SS.

Results

Fifty subjects fulfilling inclusion/exclusion criteria were enrolled into the study at visit 1. The two groups were homogeneous in demographic and clinical characteristics as summarized in Table 1. Ten patients (five placebo and five active) dropped out during the study, mostly in the first week of treatment. In the active group, three patients failed to comply with the study protocol, one retired his consent for personal reasons and one experienced worsening of symptoms. In the placebo group, one patient retired his consent and four patients had intolerable worsening of symptoms requiring more aggressive treatment. No relevant side-effect or adverse event due to the treatment was observed during the study.

Quality of life assessment

Figures 2 and 3 show the scores recorded with the Rhinasthma questionnaire. A significant difference on upper airways and lower airways scores between the two groups was shown after 4 weeks of treatment (respectively, $P=0.03$ and 0.019), whereas for the respiratory allergy impact this difference was statistically significant after 2 weeks ($P=0.046$). Also, concerning the global summary score, the difference between the groups became statistically significant after 4 weeks ($P=0.03$). Looking at

Table 1. Demography and clinical characteristics

	LCZ group	Placebo group
<i>N</i>	25	25
Sex (M/F)	11/14	9/16
Mean age (years)	32.4	37.8
Age range	16–57	16–61
Rhinoconjunctivitis alone	16	14
Rhinoconjunctivitis+actual asthma	9	11

LCZ, levocetirizine.

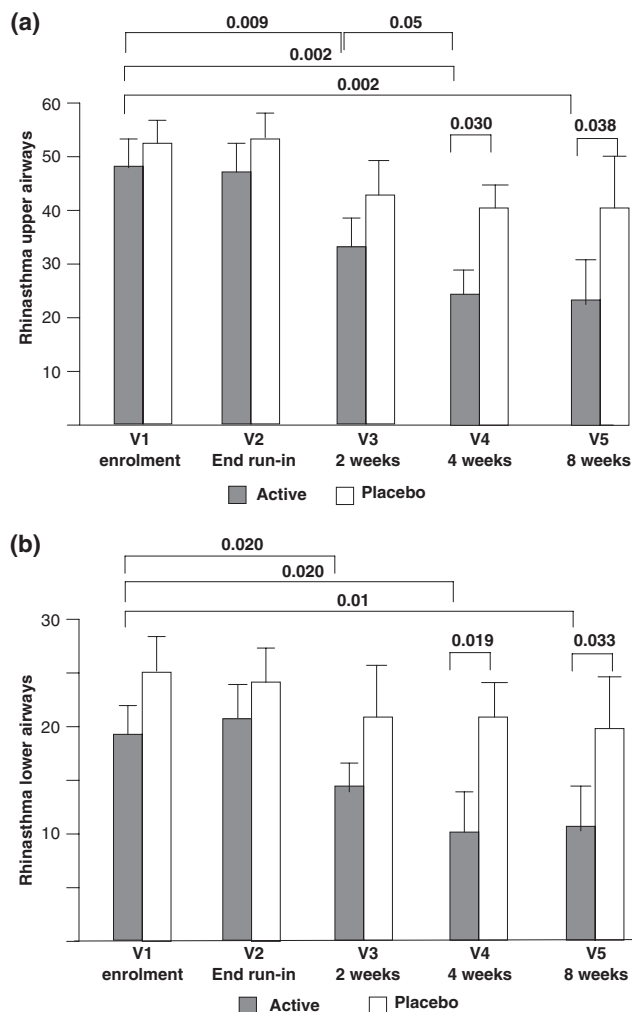


Fig. 2. (a) Rhinasthma upper airways score; (b) Rhinasthma lower airways score. The scores are shown as mean $\pm$ SEM at the various time points. Significant differences are shown on the bars.

the intra-group comparison, a significant difference vs. baseline was achieved after 2 weeks in the active group for all the considered scores and maintained throughout the whole study. No significant change was seen in the placebo group.

The SF-36 questionnaire detected a significant difference ($P < 0.05$) between active and placebo group in the following dimensions: role limitation emotional and general health at 4 weeks and bodily pain, physical functioning, role limitation physical at 4 and 8 weeks (data not shown).

Symptom scores

As summarized in Figs 4a and b, the evolution of symptom assessed weekly reflected the therapeutic effect of the active treatment. Concerning the T5SS (Fig. 4a), there was no detectable significant difference at any week

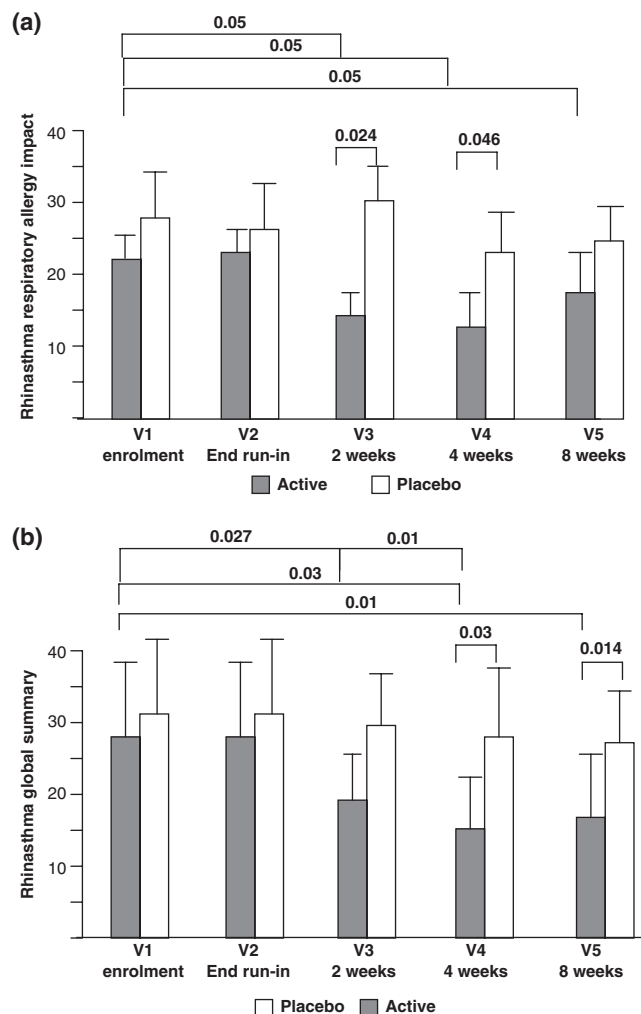


Fig. 3. (a) Rhinasthma respiratory allergy impact score; (b) Rhinasthma global score. The scores are shown as mean $\pm$ SEM at the various time points. Significant differences are shown on the bars.

vs. baseline in the placebo group, whereas symptoms improved in the active group. The improvement became significant in the second week of treatment and so remained for the whole study. The difference between groups became apparent in the second week, although not significant ($P = 0.07$), whereas in the third week significance was achieved ($P = 0.035$) and maintained throughout the whole observation period.

The small baseline difference between groups did not influence these results.

The evolution of the global (rhinitis+asthma) scores (Fig. 3b) was similar to that of T5SS, although the greater dispersion of the data reduced the significance at some time-points. The use of cromolyn was very low throughout the whole study and did not allow statistical comparison. In the asthmatic patients, the average number of doses of salbutamol was: in the active group 4.75/week at baseline and 2.35/week in the 2 months of treatment; in

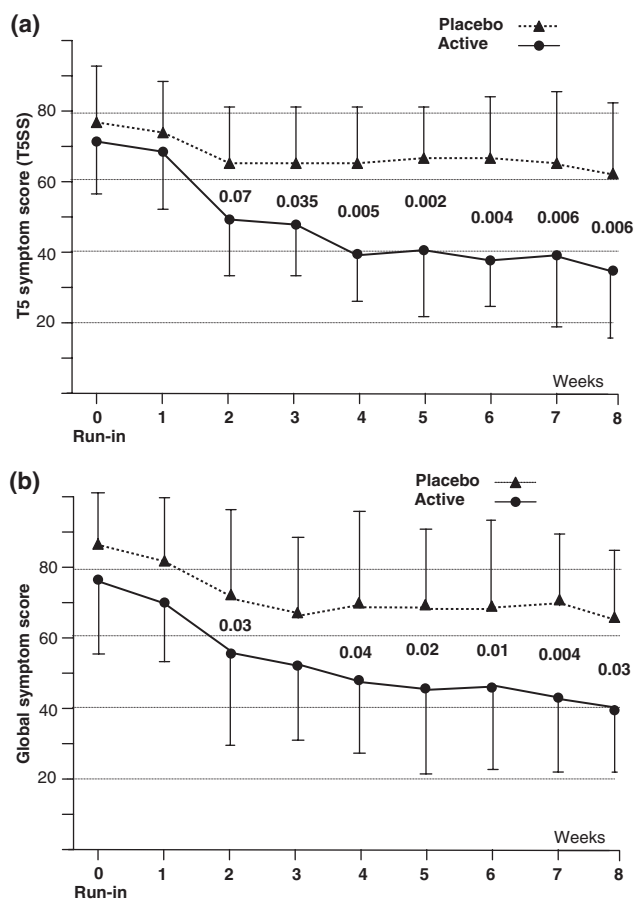


Fig. 4. (a) T5 symptoms scores; (b) global symptom score (TSS+asthma symptoms). The values are the weekly sums (mean $\pm$ SEM) in the 9 weeks of the study. The significant differences between groups at each week are shown within the graph.

the placebo group, the corresponding values were 5.2 and 5.0, with a significant difference between groups.

Nasal inflammatory parameters

Percentages of nasal eosinophils were low and highly dispersed (Fig. 5a). Nonetheless, in the active group, there was a decrease vs. baseline at 2 weeks that remained significant at all time-points, reaching $P=0.002$ at the last visit. In the placebo group, there was only a significant decrease vs. baseline in the second week, which was no longer significant at the next visits. A highly significant difference between groups ($P=0.001$) was seen in week 8. Similar results were found with neutrophils, as summarized in Fig. 5b. Neutrophils significantly decreased in the active group in the second week of treatment ($P=0.006$), whereas no significant change was seen in the placebo group. The difference between groups was statistically significant after 8 weeks of treatment ($P=0.01$). Soluble ECP and tryptase in nasal lavage fluid was always under the detection limit (2 and 1 mcg/L) in the majority of

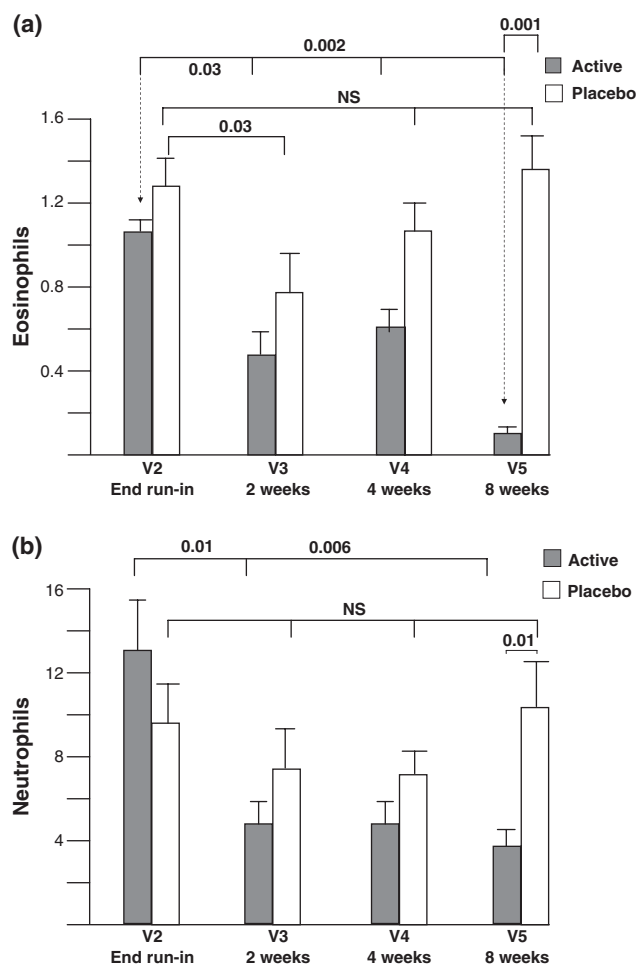


Fig. 5. (a) Eosinophils in the nasal scraping (mean $\pm$ SEM). (b) Neutrophils in the nasal scraping (mean $\pm$ SEM). Significant differences are shown on the bars.

patients, and in the remaining subjects no significant variation could be seen. The percentages of ICAM-1-positive cells at the four visits were 3.5 ± 6.9 , 2.1 ± 3.8 , 4.1 ± 9.8 and 2.5 ± 4.8 in the active group and 3.7 ± 9 , 5.7 ± 14.1 , 5.5 ± 15.5 and 5.1 ± 13.8 in the placebo group. Thus, although a reduction in the active group vs. placebo was seen, the statistical significance was not reached.

Discussion

AR (rhinoconjunctivitis) is essentially an inflammatory process, initiated by the allergen-IgE-mastcell interaction. When the exposure to the allergen is chronic, the inflammatory process also becomes chronic, and the mucosa is infiltrated by inflammatory cells. Among these cells, eosinophils are the most reliable marker of ongoing allergic inflammation, as its presence invariably correlates with all clinical, functional and immunological parameters [20]. Moreover, AR, especially in its persistent form, is often associated with asthma, as the upper and

lower airways behave identically from an immunological point of view. This is the reason why the ARIA document [2] recommends an integrated diagnostic and therapeutic approach to respiratory allergy.

An ideal drug for rhinitis should possess not only an antihistaminic effect but also additional antiinflammatory properties, and should favourably affect not only symptoms but also QoL [21, 22]. LCZ, an enantiomer of the racemic drug cetirizine, is a new antihistamine whose efficacy in AR has been repeatedly demonstrated [11, 12]. In addition, LCZ was shown to improve the QoL. Specifically, Bachert et al. [13] showed that a 6-month treatment with LCZ has a substantial effect on the QoL symptoms score and pharmacoeconomic parameters in patients with persistent AR. QoL in both rhinitis and asthma appears to correlate moderately with the clinical outcome measures. For instance, Graaf-in't Veld [23] showed a weak correlation between QoL, daily nasal symptoms and nasal hyper-reactivity in patients with perennial AR, and Marks et al. [24] revealed that changes in QoL were weakly correlated with the changes in symptoms scores. The association with change in peak-flow variability was also weak. A recent retrospective analysis of 27 randomized, controlled trials in persistent asthma [25] concluded that the impact of asthma on a patients' QoL is not fully accounted by the changes in lung function measures. Thus, QoL data complement rather than duplicate the traditional objective assessments of asthma control. Interestingly, Storms et al. [26] assessed QoL in asthmatic patients before and after seeing an allergy specialist, showing that an early intervention by the allergy specialist is more cost effective in the treatment of asthma than an intervention provided by a general practitioner.

In this study, we attempted to evaluate in a global manner the effect of LCZ in persistent AR, in particular when associated with asthma. For this reason, we choose a specific QoL questionnaire named Rhinasthma, which evaluates both the compartments (nose and bronchi) of respiratory allergy. The treatment significantly improved both upper and lower components of QoL separately and when analysed together, this supports the fact that a correct treatment of rhinitis can also improve asthma, at least as it is perceived by patients. Indeed, a possible effect of LCZ on lower airways was shown in a sub-analysis of the Xpert study [27], where rhinitis patients receiving LCZ experienced a lower number of asthma events (defined by the use of bronchodilators) compared with placebo. LCZ cannot be considered an antiasthma drug, as a direct effect on pulmonary function was not demonstrated; rather, it probably acts indirectly on lower airways by improving the nasal patency and modulating the inflammatory phenomena. In this regard, the nasal inflammatory cells were significantly decreased by the treatment, although the difference between the two groups became significant after 8 weeks of therapy. This effect cannot be

ascribed to cromolyn [28], which was rarely used as 'as-needed' therapy by all patients. This study provides the first experimental direct evidence that LCZ is effective on asthma concomitant to AR, although in the context of the 'united airway disease' [29]. This does not mean that LCZ is indicated in asthma, but certainly that the drug improves both AR and asthma, and that it is a candidate in AR patients with comorbid asthma.

The study confirms that disease-specific questionnaires are more 'sensitive' in detecting differences in QoL scores compared with the generic ones. The non-specific questionnaires, such as SF-36, usually need more enrolled patients to detect changes, especially if diseases with low impact on Health Status are considered.

In conclusion, our data substantiate a significant effect of LCZ on QoL Rhinasthma domains, on nasal inflammatory cells/parameters, and on nasal symptom scores or combined with lower airway symptoms.

Acknowledgements

This study has been partially supported by: ARMIA (Associazione Ricerca Malattie Immunologiche e Allergiche), GA²LEN, MIUR (unrestricted Educational Grant).

References

- 1 Hansen I, Klimek L, Mosges R, Hormann K. Mediators of inflammation in the early and the late phase of allergic rhinitis. *Curr Opin Allergy Clin Immunol* 2004; 4:159–63.
- 2 Bousquet J and Van Cauwenberge P (eds) Allergic Rhinitis its Impact on Asthma. *J Allergy Clin Immunol* 2001; 108 (Suppl.): S146–50.
- 3 Passalacqua G, Ciprandi G, Pasquali M, Guerra L, Canonica GW. An update on the asthma–rhinitis link. *Curr Opin Allergy Clin Immunol* 2004; 4:177–83.
- 4 Guerra S, Sherrill DN, Martinez FD. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002; 109:419–25.
- 5 Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics* 2004; 22:345–61.
- 6 Leynaert B, Neukirch C, Liard R et al. Quality of life in allergic rhinitis and asthma. *Am J Respir Crit Care Med* 2000; 162: 1391–6.
- 7 Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 2001; 108 (Suppl.):S45–53.
- 8 Kay AB. Allergy and allergic diseases. Second of two parts. *N Engl J Med* 2001; 344:109–13.
- 9 Simons FER. Advances in H1-antihistamines. *N Engl J Med* 2004; 351:2203–17.
- 10 Pagliara A, Testa B, Carrupt P-A et al. Molecular properties and pharmacokinetic behaviour of cetirizine, a zwitterionic H₁-receptor antagonist. *J Med Chem* 1998; 41:853–63.
- 11 Potter P. Levocetirizine is effective for symptom relief including nasal congestion in adolescent and adult (PAR) sensitized to house dust mites. *Allergy* 2003; 58:893–9.

- 12 Leynadier F, Mees K, Arendt C *et al.* Efficacy and safety of levocetirizine in seasonal allergic rhinitis. *Acta Otorhinolaryngol Belg* 2001; **55**:305–12.
- 13 Bachert C, Bousquet J, Canonica GW *et al.* Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol* 2004; **114**:838–44.
- 14 Mollimard M, Diquet B, Benedetti MS. Comparison of pharmacokinetics and metabolism of desloratadine, fexofenadine, levocetirizine, and mizolastine in humans. *Fundam Clin Pharmacol* 2004; **18**:399–411.
- 15 Baiardini I, Pasquali M, Giardini A *et al.* Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. *Allergy* 2003; **58**:289–94.
- 16 Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention. National Heart, Lung and Blood Institute, National Institute of Health, Bethesda, MD, 1997, NIH Publication no. 96-3659B.
- 17 Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991; **21**:77–83.
- 18 Ciprandi G, Pronzato C, Ricca V, Varese P, Del Giacco GS, Canonica GW. Terfenadine exerts antiallergic activity reducing ICAM1 expression on nasal epithelial cells in patients with pollen allergy. *Clin Exp Allergy* 1995; **25**:871–8.
- 19 Belda J, Parameswaran K, Keith PK, Hargreave FE. Repeatability and validity of cell and fluid-phase measurements in nasal fluid: a comparison of two methods of nasal lavage. *Clin Exp Allergy* 2001; **31**:1111–5.
- 20 Ciprandi G, Vizzaccaro A, Cirillo I, Tosca M, Massolo A, Passalacqua G. Nasal eosinophils display the best correlation with symptoms, pulmonary function and inflammation in allergic rhinitis. *Int Arch Allergy Immunol* 2005; **136**:266–72.
- 21 Bousquet J, Van Cauwenberge P, Bachert C, Canonica GW, Demoly P *et al.* Requirements for medications commonly used in the treatment of allergic rhinitis. European Academy of Allergy and Clinical Immunology (EAACI), Allergic Rhinitis and its Impact on Asthma (ARIA). *Allergy* 2003; **58**:192–7.
- 22 Holgate ST, Canonica GW, Simons FE *et al.* Consensus group on new-generation antihistamines. Consensus Group on New-Generation Antihistamines (CONGA): present status and recommendations. *Clin Exp Allergy* 2003; **33**:1305–24.
- 23 de Graaf-in 't Veld T, Koenders S, Garrelds IM, Gerth van Wijk R. The relationships between nasal hyperreactivity, quality of life, and nasal symptoms in patients with perennial allergic rhinitis. *J Allergy Clin Immunol* 1996; **98**:508–13.
- 24 Marks GB, Dunn SM. An evaluation of an asthma quality of life questionnaire as a measure of change in adults with asthma. *J Clin Epidemiol* 1993; **46**:1103–11.
- 25 Carranza Rosenzweig KR, Edwards L, Lincourt W, Dorinsky P, ZuWallack RL. The relationship between health-related quality of life, lung function and daily symptoms in patients with persistent asthma. *Respir Med* 2004; **98**:1157–65.
- 26 Storms B, Olden L, Nathan R, Bodman S. Effect of allergy specialist care on the quality of life in patients with asthma. *Ann Allergy Asthma Immunol* 1995; **75**:491–4.
- 27 Bachert C, Demarteau N. Levocetirizine reduces asthma comorbidity in patients with persistent allergic rhinitis: an exploratory analysis of the XPERTTM trial. *Allergy Clin Immunol Int* 2005; **S1**:100 (abstract 238).
- 28 Sensi LG, Seri A, Siracusa A, Marcucci F. Allergic rhinitis in children: effects of flunisolide and disodium cromoglycate on nasal eosinophil cationic protein. *Clin Exp Allergy* 1997; **27**:270–6.
- 29 Passalacqua G, Ciprandi G, Canonica GW. United airways disease: therapeutic aspects. *Thorax* 2000; **55** (Suppl.):S26–7.