

The Loss of Smell in Persistent Allergic Rhinitis Is Improved by Levocetirizine due to Reduction of Nasal Inflammation but Not Nasal Congestion (the CIRANO Study)

José Maria Guilemany^{a, d} Alfons García-Piñero^{a, d} Isam Alobid^{a, d}
Silvia Centellas^{a, d} Franklin Santiago Mariño^a Antonio Valero^{b, d}
Manuel Bernal-Sprekelsen^{a, d} César Picado^{b–d} Joaquim Mollo^{a, c, d}

^aRhinology Unit and Smell Clinic, Department of Otorhinolaryngology, Head and Neck Surgery, and

^bDepartment of Pneumology and Respiratory Allergy, Hospital Clínic i Universitari de Barcelona,

^cInstitut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), and ^dCIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

Key Words

Olfaction • Levocetirizine • Persistent allergic rhinitis

Abstract

Background: Persistent allergic rhinitis (PER) has a moderate impact on the sense of smell, but no controlled study has reported the effect of antihistamines on the loss of smell in patients with PER. **Methods:** Patients with PER and subjective loss of the sense of smell ($n = 27$) were included in this pilot randomised, double-blind, placebo-controlled study. Nasal symptoms, nasal endoscopy, skin prick test, acoustic rhinometry, peak nasal inspiratory flow, nasal nitric oxide (nNO), and olfactometry (Barcelona Smell Test-24; BAST-24) were performed and evaluated in all PER patients at baseline and after 7 and 30 days of treatment with levocetirizine 5 mg or placebo. **Results:** The study population was randomized into two homogeneous groups: levocetirizine ($n = 14$) and placebo groups ($n = 13$). The evolution of symptoms reflected the therapeutic effect of levocetirizine treatment on rhinorrhea, nasal itching, eye itching, sneezing, and the total symptoms score after 7 and 30 days. Significant improvement in loss of smell by a visual analog scale (VAS) was ob-

served after 7 days of levocetirizine treatment (7.2 ± 4.3 ; $p < 0.05$) compared to placebo (-9.4 ± 6.2). Improvement in smell identification by BAST-24 was strongly correlated ($r = 0.72$; $p < 0.05$) with smell improvement by VAS after 30 days. After 7 days of treatment with levocetirizine, the nNO values decreased (-494 ± 188) compared to placebo (155 ± 284 ppb; $p < 0.05$). **Conclusions:** The CIRANO study suggests that levocetirizine is effective on PER symptoms, including a transient improvement in loss of smell, and that this improvement concurs more with reduction of nasal inflammation than of nasal patency.

Copyright © 2012 S. Karger AG, Basel

Introduction

An estimated 5–30% of the general worldwide population suffers from allergic rhinitis (AR) [1]. AR is an inflammatory disease affecting the nasal mucosa with a considerable impact on the quality of life (QoL) (work,

J.M.G. and A.G.-P. contributed equally to this work as first authors.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2012 S. Karger AG, Basel
1018–2438/12/1582–0184\$38.00/0

Accessible online at:
www.karger.com/iaa

Correspondence to: Dr. José Maria Guilemany
Rhinology Unit and Smell Clinic, Department of Otorhinolaryngology,
Head and Neck Surgery, Hospital Clínic i Universitari de Barcelona
c/ Villarroel, 170, ES-08036 Barcelona (Spain)
Tel. +34 932 279 872, E-Mail guilemany@gmail.com

school, and social life) of the sufferer. Classically, AR was divided into seasonal (SAR) and perennial (PAR). Nowadays, using ARIA criteria, AR is divided into persistent (PER) or intermittent AR (IAR) [2].

Although several studies have reported smell disorders associated with SAR [3–9], few studies have addressed the potential loss of smell in patients with PAR [8, 9]. It is well known that the association between AR and chronic rhinosinusitis seriously harms the sense of smell [10, 11]. Smell disorders are present in 21–23% of patients with AR [12, 13], but 31% of patients with AR have gustative upsets [13]. A study documented the moderate loss of smell (15%) after allergen exposure, with 70% nasal narrowing [3]. We recently published the first study using ARIA criteria in patients with PER, which concluded that this disease induces a moderate loss of smell, with a higher impairment in those with self-reported hyposmia (SRH) and moderate-to-severe PER [14].

Few controlled studies [6, 15], all done in SAR, have investigated the effect of antihistamines improving the sense of smell and nasal congestion in AR. Levocetirizine is a potent second generation nonsedative H₁-antagonist used in the treatment of AR and urticaria. The XPERT study demonstrated that levocetirizine improves nasal symptoms [16] and QoL [17] and reduces socioeconomic costs [18] in patients with PER, with an incidence of side effects similar to that of placebo. Compared to other anti-H₁, levocetirizine possesses a very favorable pharmacokinetic and pharmacodynamic profile with high selectivity for the H₁-receptor, a low volume of distribution, and virtually no liver metabolism or drug-to-drug interaction [19]. In patients with PAR, a randomized, double-blind, placebo-controlled study comparing levocetirizine and loratadine demonstrated a significant improvement in nasal symptoms (83.8 vs. 66.7% of patients) compared to placebo [20]. To date, no controlled study has reported the effect of antihistamines on the sense of smell, nasal inflammation, and nasal congestion in patients with PER.

However, the nature of odor identification, closely related to familiar and cultural aromatic items, usually limits the use of olfactory tests to the country or region where they have been developed and validated. So far, the Barcelona Smell Test-24 (BAST-24) [21], a smell test validated for the Spanish and Mediterranean population, has been used to evaluate the loss of smell [14] in PER patients, showing a link between the magnitude of smell disorders and the severity of AR.

Material and Methods

Population and Design

Study Population

From a population of 49 patients with PER, 27 consecutive patients with SRH were included in this randomized, double-blind, placebo-controlled study. Inclusion criteria for the patients were a history of PER (at least 2 years), according to ARIA [2] duration and severity criteria, with SRH. Exclusion criteria were the existence of any nasal disease other than PER: IAR, acute or chronic rhinosinusitis, specific immunotherapy during the 3 years before the study, age under 18 years, pregnancy, antiallergic therapy at study entry, presence of parasitic infections, hypereosinophilia syndrome, or refusal to consent.

Study Design

Patients with AR were evaluated for PER (symptoms present for more than 4 days a week and for more than 4 consecutive weeks) following ARIA guidelines [2]. The primary objective of this double-blind placebo-controlled trial was to assess the efficacy of 5 mg levocetirizine dihydrochloride tablets administered once daily at bedtime for 4 weeks compared to placebo to improve the sense of smell, by using the Barcelona Smell Identification Test (BAST-24), in PER patients. Secondary objectives were to assess the efficacy after 7 days of treatment and at the end of the treatment period (30 days) on nasal symptoms including loss of smell, as well as nasal permeability and patency [acoustic rhinometry, peak nasal inspiratory flow (PNIF) monitoring], nasal inflammation (nasal nitric oxide; nNO), QoL (Rhinoconjunctivitis Quality of Life Questionnaire; RQLQ), and safety after 4 weeks of levocetirizine or placebo treatment.

Nasal symptoms, nasal endoscopy, skin prick test, acoustic rhinometry, PNIF, nNO, and olfactometry (BAST-24) were performed and evaluated in all PER patients. Patients were allowed to use nasal saline washes during a 4-week washout period for oral and intranasal steroids, a 2-week period for antileukotrienes, and 7 days for antihistamines. The Ethics Committee of our institution approved the study, and signed informed consent was obtained from all patients.

Outcome Assessment

Allergy Study

Skin prick tests were performed using commercial extracts against the main airborne allergens present in our geographic area.

Nasal Endoscopy

Mucopurulent discharge from the middle meatus, edema/mucosal obstruction primarily in the middle meatus, and nasal polyps were evaluated for exclusion criteria.

Nasal Symptoms

Loss of the sense of smell and the global rhinitis score (GRS) were assessed using a visual analog scale (VAS; 0–10 cm). In addition, nasal congestion, rhinorrhea, nasal and eye itching, sneezing, and the Total 4 Symptoms Score (T4SS; sneezing, rhinorrhea, nasal and ocular pruritus) were assessed using a Likert scale (0–3). All symptoms were assessed at baseline and after 7 and 30 days of treatment.

Table 1. Demographic data on PER patients with SRH

	All patients	Placebo	Levocetirizine, 5 mg
Patients, n (%)	27 (100)	13 (48.1)	14 (51.9)
Mean age $\pm$ SEM, years	31.9 $\pm$ 2	32.6 $\pm$ 2.8	31.1 $\pm$ 2.9
Females, n (%)	13 (48.1)	6 (46.2)	7 (50)
PER severity			
Mild, n (%)	4 (14.8)	3 (23.0)	1 (7.1)
Moderate/severe, n (%)	23 (85.2)	10 (77.0)	13 (92.9)

Olfactory Function

Olfactometry was assessed at baseline and after 7 and 30 days of treatment by means of the BAST-24 [21] using 20 odors for the olfactory nerve. The smell test was performed in a quiet, noise-isolated, well-ventilated room with controlled humidity (40–70%) and temperature (21–23°C). All of the odorants were located in hermetic glass jars. The explorer and the patients did not wear perfumes, lotions, or creams on the day of the examination. The odorant jar had to stay at 1 cm from the nose and there was no contact between the explorer's finger and the patient's face.

Nasal Function

Nasal airflow was monitored (at baseline, 7 and 30 days) by peak nasal inspiratory flow (PNIF). The test was repeated 3 times and the best result was reported. Using acoustic rhinometry, the nasal volume from 0 to 6 cm (V_{0-6}) and the minimum cross-sectional area (MCA), assessed at baseline and after 7 and 30 days of treatment, were measured from each nasal cavity within the distance of 6 cm from the nostrils. The test was repeated 3 times, and the mean of MCA and volume (V_{0-6}) of the nasal cavities were calculated [22].

Nasal Inflammation

nNO was used as a noninvasive marker of upper airway inflammation [23]. nNO was assessed at baseline and after 7 and 30 days of treatment. A nasal sample was obtained from one nostril using a negative pressure pump with a flow rate of 3 liters/min. Patients were instructed to blow up their cheeks to elevate the mouth pressure in order to lift up the palate and isolate the nasal cavity from the rest of respiratory system. nNO was measured when the levels reached plateau values.

Quality of Life

The RQLQ is a disease-specific, validated, and reproducible instrument for evaluating QoL on the basis of how symptoms and treatments affect each patient's physical, social, and emotional well-being. It includes 28 items distributed in 7 domains. All items are scored ranging from 0 (no impairment) to 6 (major impairment). The RQLQ was assessed at baseline and after 7 and 30 days of treatment. A reduction in score of 0.5 or greater was considered clinically important [24]. The differences between baseline and 7 days (Δ_{0-7}) and 30 days (Δ_{0-30}) were calculated for all of the measurements between levocetirizine and placebo.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows (SPSS 11.0; Chicago, Ill., USA). All analyses were performed using two-tailed tests with significance at the $p < 0.05$ level, and data are presented as means $\pm$ SEM. Descriptive analysis was carried out for the demographic characteristics, and a comparative analysis between groups was performed using the χ^2 test. Comparative intergroup and intragroup analyses were performed using nonparametric tests: Wilcoxon and Mann-Whitney tests were used for paired and unpaired samples, respectively.

Results

Allergy Study

All patients diagnosed with PER and SRH had a positive skin prick test to house dust mites (100%). Other allergen positivities were present against animal dander (30.7%) and pollens (27%).

Demographic Data

A total of 27 patients (13 women, mean age 31.9 ± 2 years) were enrolled into this study from January 2005 to February 2007. Most of them (23 patients, 85.2%) were classified as having moderate/severe PER, while only 4 patients (14.8%) were classified as having mild PER. The study population was randomized into two groups: the group treated with levocetirizine 5 mg consisted of 14 patients (7 women, mean age 31.1 ± 2.9 years) and the placebo group consisted of 13 patients (6 women, mean age 32.6 ± 2.8 years). The two groups were homogeneous in terms of their demographic characteristics as summarized in table 1.

Nasal Symptoms

Compared to placebo, treatment with levocetirizine induced significant ($p < 0.05$) improvement in nasal itching (at 7 days) and sneezing (at 30 days) (table 2), and on T4SS (at 7 days) (fig. 1a) and the GRS (at 7 and 30 days) (fig. 1b).

Olfactory Function

Significant improvement in loss of smell by VAS was observed with levocetirizine (7.2 ± 4.3 ; $p < 0.05$) compared to placebo (-9.4 ± 6.2) after 7 days but not 30 days (fig. 2). Although patients treated with levocetirizine scored better on smell detection, identification, and forced choice by BAST-24 than those treated with placebo after 7 days, the differences did not reach statistical significance (table 3). However, smell identification by BAST-24 and loss of smell by VAS after 30 days were strongly correlated ($r = 0.72$; $p < 0.05$).

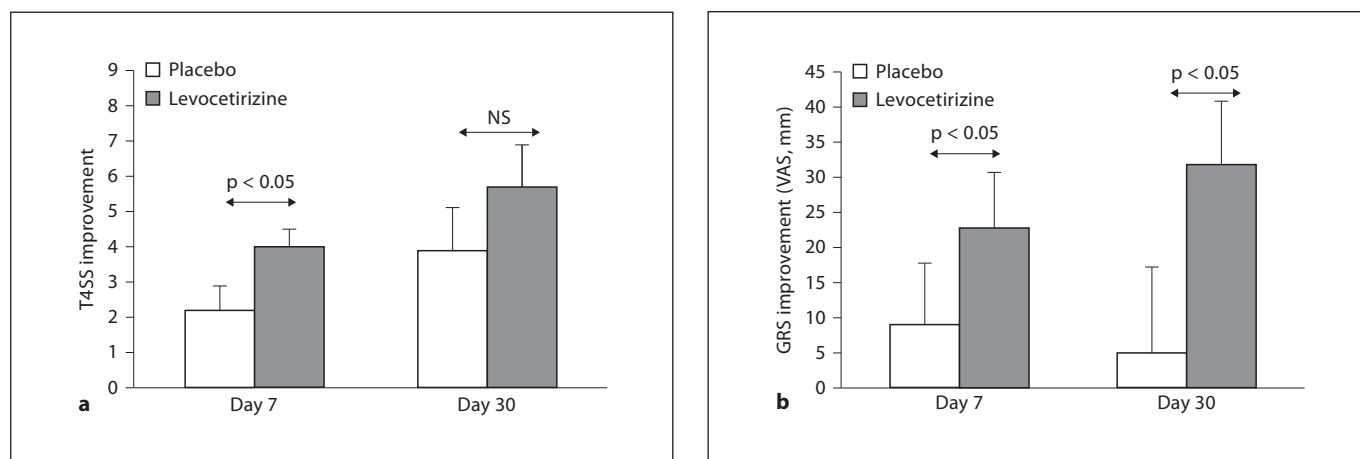


Fig. 1. Effect of levocetirizine 5 mg on nasal symptoms in PER patients. Improvement of the T4SS at 7 days (**a**) and the GRS after 7 and 30 days (**b**). $p < 0.05$, compared to placebo (Mann-Whitney test).

Table 2. Effect of levocetirizine and placebo on nasal symptoms in PER patients

Symptoms	Time	Placebo	Levocetirizine 5 mg
Nasal congestion	B	2.5 ± 0.1	2.4 ± 0.2
	Δ_{0-7}	-0.4 ± 0.2	-0.5 ± 0.3
	Δ_{0-30}	-0.8 ± 0.3	-0.8 ± 0.4
Rhinorrhea	B	2.1 ± 0.2	2.5 ± 0.2
	Δ_{0-7}	-0.7 ± 0.2	-1 ± 0.2
	Δ_{0-30}	-1.1 ± 0.3	-1.1 ± 0.3
Nasal itching	B	1.9 ± 0.3	2.4 ± 0.2
	Δ_{0-7}	0.2 ± 0.2	$-0.9 \pm 0.2^*$
	Δ_{0-30}	-0.6 ± 0.3	-1.2 ± 0.2
Eye itching	B	1.6 ± 0.3	1.1 ± 0.3
	Δ_{0-7}	-0.7 ± 0.2	-0.5 ± 0.2
	Δ_{0-30}	-1 ± 0.4	-0.5 ± 0.1
Sneezing	B	1.5 ± 0.2	2.5 ± 0.2
	Δ_{0-7}	-0.3 ± 0.2	-1 ± 0.2
	Δ_{0-30}	-0.4 ± 0.3	$-1.4 \pm 0.3^*$

B = Baseline; Δ = symptom differential (between baseline and 7 or 30 days).

* $p < 0.05$, compared to placebo (Mann-Whitney test).

Nasal Function

After 7 days, there was an improvement, although without statistical significance, in nasal patency monitored by either PNIF or acoustic rhinometry (MCA, volume 0–6) in patients treated with levocetirizine 5 mg compared to placebo (table 4).

Nasal Nitric Oxide

In PER patients, at baseline, the nNO values were higher ($1,467.5 \pm 235$ ppb) than the normal values [23]. The nNO values decreased after 7 days of treatment with levocetirizine (-494 ± 188) compared to placebo (155 ± 284 ppb; $p < 0.05$) (fig. 3). Similar results were obtained after 30 days but without reaching statistical significance. After 7 days, nNO levels were correlated ($r = 0.66$; $p < 0.05$) with smell identification by BAST-24.

Quality of Life

After 7 days, the evolution of QoL showed an improvement with levocetirizine 5 mg compared to placebo ($p = 0.06$) in eye symptoms and emotional function (table 5). After 30 days, the improvement of activities on the RQLQ was correlated with the improvement of the loss of smell by VAS ($r = 0.66$; $p < 0.05$). Improvement in the RQLQ was also correlated with improvement of smell identification by BAST-24 ($r = 0.78$; $p < 0.01$).

Safety Evaluations

Both groups had similar safety profiles. No relevant adverse events due to the treatment were reported during the study.

Discussion

This study is the first to describe the improvement in the sense of smell in patients with PER after levocetirizine treatment compared to placebo. The major findings of

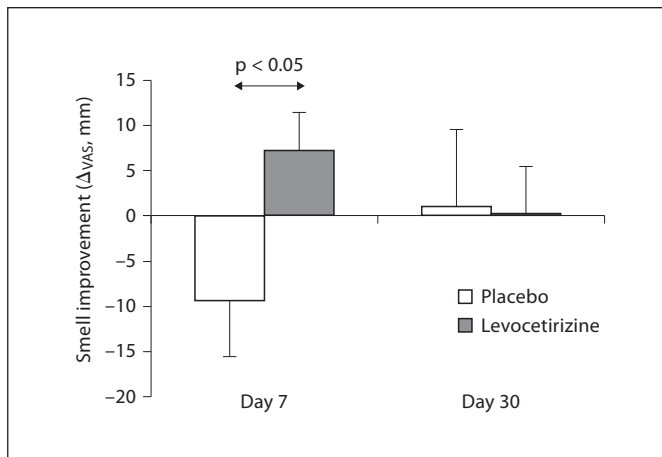


Fig. 2. Effect of levocetirizine 5 mg on the loss of smell in PER patients. Improvement of smell by VAS after 7 and 30 days. $p < 0.05$, compared to placebo (Mann-Whitney test).

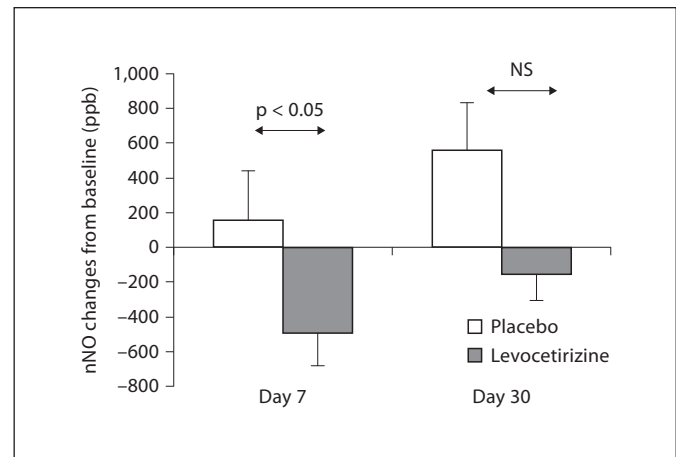


Fig. 3. Effect of levocetirizine 5 mg on nasal inflammation in PER patients. Improvement of nNO levels (ppb) after 7 and 30 days. $p < 0.05$, compared to placebo (Mann-Whitney test).

Table 3. Effect of levocetirizine compared to placebo on the sense of smell by BAST-24 in PER patients

BAST-24	Time	Placebo	Levocetirizine 5 mg
Detection	B	97.3 ± 1.9	99.2 ± 0.7
	Δ_{0-7}	$+0.9 \pm 0.6$	$+0.4 \pm 0.4$
	Δ_{0-30}	$+1 \pm 0.6$	$+0.5 \pm 0.4$
Identification	B	37 ± 5.6	43.1 ± 5
	Δ_{0-7}	$+1.3 \pm 5.4$	$+11.2 \pm 5.2$
	Δ_{0-30}	$+7.5 \pm 7$	$+3.6 \pm 3.1$
Forced choice	B	67.3 ± 4.9	67.7 ± 5.2
	Δ_{0-7}	$+6.4 \pm 6$	$+1.7 \pm 2.2$
	Δ_{0-30}	$+11.5 \pm 4.2$	$+2.7 \pm 3.6$

B = Baseline; Δ = smell differential (between baseline and 7 or 30 days).

$p < 0.05$, compared to placebo (Mann-Whitney test).

Table 4. Effect of levocetirizine compared to placebo on nasal function in PER patients

Nasal patency test	Time	Placebo	Levocetirizine 5 mg
PNIF, l/min	B	89.7 ± 11.4	87.8 ± 12.6
	Δ_{0-7}	$+11.4 \pm 5.7$	$+20 \pm 11.1$
	Δ_{0-30}	$+22.6 \pm 10.1$	$+20.4 \pm 12.8$
Acoustic rhinometry MCA, cm ²	B	1.2 ± 0.4	0.7 ± 0.1
	Δ_{0-7}	-0.13 ± 0.14	$+0.43 \pm 0.4$
	Δ_{0-30}	-0.31 ± 0.27	-0.01 ± 0.02
Volume 0–6, cm ³	B	11.9 ± 1	11.8 ± 2.1
	Δ_{0-7}	-0.6 ± 1.3	$+1.68 \pm 2.3$
	Δ_{0-30}	$+1.53 \pm 1.1$	$+1.08 \pm 1$

B = Baseline; Δ = smell differential (between baseline and 7 or 30 days); MCA = minimum cross-sectional area.

$p < 0.05$, compared to placebo (Mann-Whitney test).

the present study in PER patients were: (1) levocetirizine improves the loss of smell by VAS, but not by BAST-24, after 7 days of treatment; (2) levocetirizine improves nasal itching, sneezing, and the GRS score after 7 and 30 days of treatment; (3) levocetirizine improves nasal inflammation (nNO) after 7 days of treatment; (4) levocetirizine improves QoL in PER at 7 days, and (5) the improvement of smell by levocetirizine correlated with the decrease in nasal inflammation but not with the improvement of nasal obstruction.

These results support the hypothesis that levocetirizine, in addition to nasal symptoms and QoL, is also able to improve temporarily the loss of smell in PER patients, with assessment of the sense of smell by VAS being more sensitive to changes than subjective olfactometry (BAST-24).

Few studies have previously reported smell disorders in patients with SAR [3–9] and PAR [8, 9] linked to inflammation and not to nasal obstruction. Using ARIA criteria, we demonstrated in a previous study that PER

Table 5. Effect of levocetirizine compared to placebo on QoL in PER patients

RQLQ domains	Time	Placebo	Levocetirizine 5 mg
Activity limitations	B	4.3 ± 0.4	4.7 ± 0.3
	Δ ₀₋₇	-0.5 ± 0.4	-1.6 ± 0.4
	Δ ₀₋₃₀	-1.2 ± 0.6	-2 ± 0.6
Sleep problems	B	2.8 ± 0.4	3 ± 0.3
	Δ ₀₋₇	-0.16 ± 0.3	-1 ± 0.3
	Δ ₀₋₃₀	-1.1 ± 0.3	-1.7 ± 0.3
General symptoms	B	2.8 ± 0.4	3 ± 0.3
	Δ ₀₋₇	-0.12 ± 0.3	-0.9 ± 0.3
	Δ ₀₋₃₀	-0.36 ± 0.3	-1 ± 0.3
Practical problems	B	4.2 ± 0.5	3.8 ± 0.4
	Δ ₀₋₇	-0.36 ± 0.2	-1 ± 0.4
	Δ ₀₋₃₀	-1.36 ± 0.5	-1.25 ± 0.6
Nasal symptoms	B	3.7 ± 0.4	4.1 ± 0.3
	Δ ₀₋₇	-0.3 ± 0.4	-1 ± 0.4
	Δ ₀₋₃₀	-0.9 ± 0.5	-1.45 ± 0.5
Eye symptoms	B	2.2 ± 0.5	1.8 ± 0.5
	Δ ₀₋₇	-0.3 ± 0.3	-1.8 ± 0.7 [†]
	Δ ₀₋₃₀	-0.4 ± 0.4	-1.9 ± 0.7
Emotional function	B	2.4 ± 0.4	2.2 ± 0.3
	Δ ₀₋₇	-0.1 ± 0.3	-0.65 ± 0.2 [†]
	Δ ₀₋₃₀	-0.2 ± 0.3	-1 ± 0.4
Total	B	3.2 ± 0.3	3.2 ± 0.2
	Δ ₀₋₇	-0.3 ± 0.2	-0.9 ± 0.2
	Δ ₀₋₃₀	-0.8 ± 0.3	-1.3 ± 0.4

B = Baseline; Δ = differential quality of life (between baseline and 7 or 30 days).

[†] p = 0.06, compared to placebo (Mann-Whitney test).

induces a moderate loss of smell [14]. However, patients with PER and SRH were mainly linked to moderate-severe disease. Thus, a simple question about the patient's sense of smell may be a reasonable guide in defining the severity of PER.

Levocetirizine is a potent H₁-receptor antagonist with proven efficacy in both SAR and PAR, as well as in PER. In the XPERT [16–18] study, a 6-month, double-blind, placebo-controlled multicenter trial of 551 patients with PER who received levocetirizine (5 mg/day) or placebo, levocetirizine significantly improved nasal and ocular symptoms from the first week, while nasal congestion only improved after 5 weeks of treatment. Our study also showed that levocetirizine significantly improved nasal itching, sneezing, the total symptoms score, and the GRS by VAS. As in the XPERT study, our data did not show an

improvement in nasal congestion after 1 month of treatment with levocetirizine.

A recent study (ACCEPT-2) [25] demonstrated that desloratadine was effective in reducing the total symptom burden and individual symptom scores associated with PER, with a safety profile similar to that of placebo, as has been shown before for IAR (ACCEPT-1) [26]. Improvements were also noted in various measures of QoL (RQLQ) and school/work productivity. In opposition to our data, the ACCEPT-2 study showed an improvement in nasal congestion after 29 days of treatment with desloratadine. In PER patients, rupatadine and cetirizine were also significantly more effective than placebo on nasal symptoms at 4 and 8 weeks, but only rupatadine showed significant differences with placebo on nasal symptoms at 12 weeks [27]. A significant relief of nasal obstruction was not observed for any of the active treatments when compared to placebo.

In our study, levocetirizine improved the loss of smell by VAS but not by BAST-24. In spite of the sample size, it is clear that loss of smell by VAS is more sensitive than the BAST-24 in detecting an improvement in the sense of smell.

The pathogenesis of olfactory dysfunction in AR is not fully understood. Patients with AR have shown a close correlation between the loss of smell and inflammatory markers such as eosinophilic cationic protein (ECP) [5] and blood eosinophils [12]. In fact, treatment with intra-nasal steroids improves the loss of smell in AR patients [15]. A previous study [14] suggested that the loss of smell in PER patients may have a mixed etiology in which two main factors may be responsible, nasal obstruction and nasal inflammation. In the present study, the olfactory improvement after levocetirizine seems to be more related to anti-inflammatory changes measured by nNO than to nasal patency changes. The small number of patients in this pilot study could be the reason for the lack of significance in nasal patency. However, there were strong correlations between the improvement of smell identification by BAST-24 and the improvement of loss of smell by VAS, QoL by RQLQ, and nasal inflammation by nNO. In PER patients, this is the first study to demonstrate the anti-inflammatory effect of levocetirizine in nasal inflammation measured by a noninvasive technique (nNO). No permeability changes measured by PNIF and acoustic rhinometry were observed in the group of levocetirizine compared to placebo.

In the XPERT study [17], treatment with levocetirizine significantly improved the RQLQ overall score from week 1 to 6 months, compared to placebo. Analyses of the

RQLQ individual domain scores showed that activities, practical problems, nasal symptoms, and eye symptoms were the most impaired. In our study we did not find this improvement in the RQLQ overall score after levocetirizine treatment and we only found an improvement in eye symptoms and emotional function after 1 month with levocetirizine treatment.

In conclusion, the CIRANO study shows that levocetirizine is effective against PER symptoms including the improvement of the sense of smell. The study also sug-

gests that the temporary improvement of loss of smell after levocetirizine treatment is linked to changes in nasal inflammation but not nasal patency and occurs mainly in the early stages of treatment.

Acknowledgment

This work was financially supported by UCB Pharma.

References

- Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H, ISAAC Phase Three Study Group: World-wide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–743.
- Bousquet J, Khaltaev N, Cruz A, Denburg J, Fokkens W, Togias A, et al: ARIA update (in collaboration with GA²LEN and AllerGen). *Allergy* 2008;63:8–160.
- Lane AP, Zweiman B, Lanza DC, Swift D, Doty R, Dhong HJ, Kennedy DW: Acoustic rhinometry in the study of the acute nasal allergic response. *Ann Otol Rhinol Laryngol* 1996;105:811–818.
- Hinriksdottir I, Murphy C, Bende M: Olfactory threshold after nasal allergen challenge. *ORL J Otorhinolaryngol Relat Spec* 1997;59:36–38.
- Klimek L, Eggers G: Olfactory dysfunction in allergic rhinitis is related to nasal eosinophilic inflammation. *J Allergy Clin Immunol* 1997;100:158–164.
- Meltzer EO, Jalowayski AA, Orgel HA, Harris AG: Subjective and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. *J Allergy Clin Immunol* 1998;102:39–49.
- Simola M, Malmberg H: Sense of smell in allergic and nonallergic rhinitis. *Allergy* 1998;53:190–194.
- Moll B, Klimek L, Eggers G, Mann W: Comparison of olfactory function in patients with seasonal and perennial allergic rhinitis. *Allergy* 1998;53:297–301.
- Apter AJ, Mott AE, Frank ME, Clive JM: Allergic rhinitis and olfactory loss. *Ann Allergy Asthma Immunol* 1995;75:311–316.
- Apter AJ, Gent JF, Frank ME: Fluctuating olfactory sensitivity and distorted odor perception in allergic rhinitis. *Arch Otolaryngol Head Neck Surg* 1999;125:1005–1010.
- Cowart BJ, Flynn-Rodden K, McGready SL: Hyposmia in allergic rhinitis. *J Allergy Clin Immunol* 1993;91:747–751.
- Rydzewski B, Pruszevicz A, Sulkowski WJ: Assessment of smell and taste in patients with allergic rhinitis. *Acta Otolaryngol* 2000;120:323–326.
- Higo R, Ichimura K, Ota Y, Ishizuka T, Shimazaki Y: Investigation of 'anosmic zones' associated with nasal allergy (in Japanese). *Nippon Jibiinkoka Gakkai Kaiho* 1996;99:1648–1652.
- Guilemany JM, García-Piñero A, Alobid I, Cardelus S, Centellas S, Bartra J, Valero A, Picado C, Mullol J: Persistent allergic rhinitis has a moderate impact on the sense of smell depending on both nasal congestion and inflammation. *Laryngoscope* 2009;119:233–238.
- Hilberg O: Effect of terfenadine and budesonide on nasal symptoms, olfaction, and nasal airway patency following allergen challenge. *Allergy* 1995;50:683–688.
- Bachert C, Bousquet J, Canonica GW, Durham SR, Klimek L, Mullol J, Van Cauwenberge PB, Van Hammée G, XPERT Study Group: Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol* 2004;114:838–844.
- Walter Canonica G, Bousquet J, Van Hammée G, Bachert C, Durham SR, Klimek L, Mullol J, Van Cauwenberge PB, XPERT Study Group: Levocetirizine improves health-related quality of life and health status in persistent allergic rhinitis. *Respir Med* 2006;100:1706–1715.
- Bousquet J, Demarteau N, Mullol J, van den Akker-van Marle ME, Van Ganse E, Bachert C, XPERT study group: Costs associated with persistent allergic rhinitis are reduced by levocetirizine. *Allergy* 2005;60:788–794.
- Devalia JL, De Vos C, Hanotte F, Baltes E: A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb 28557 on histamine-induced cutaneous responses in healthy adult volunteers. *Allergy* 2001;56:50–57.
- Stübner P, Zieglmayer R, Horak F: A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit – the Vienna Challenge Chamber (VCC). *Curr Med Res Opin* 2004;20:891–902.
- Cardesin A, Alobid I, Benítez P, Sierra E, de Haro J, Bernal-Sprekelsen M, Picado C, Mullol J: Barcelona Smell Test-24 (BAST-24): validation and smell characteristics in the healthy Spanish population. *Rhinology* 2006;44:83–89.
- Serrano C, Valero A, Bartra J, Torrego T, Mullol J, Picado C: Effects on nasal nitric oxide production of 2 mechanisms of vasoconstriction. *J Investig Allergol Clin Immunol* 2007;17:337–340.
- Valero A, Serrano C, Valera JL, Barberá A, Torrego A, Mullol J, Picado C: Nasal and bronchial response to exercise in patients with asthma and rhinitis: the role of nitric oxide. *Allergy* 2005;60:1126–1131.
- Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ: Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996;98:843–845.
- Bousquet J, Bachert C, Canonica GW, Mullol J, Van Cauwenberge P, Bindeslev Jensen C, Fokkens WJ, Ring J, Keith P, Lorber R, Zuberbier T, ACCEPT-2 study group: Efficacy of desloratadine in persistent allergic rhinitis: a GA²LEN study. *Int Arch Allergol Immunol* 2010;153:395–402.
- Bousquet J, Bachert C, Canonica GW, Mullol J, Van Cauwenberge P, Bindeslev Jensen C, Fokkens WJ, Ring J, Keith P, Lorber R, Zuberbier T, ACCEPT-1 study group: Efficacy of desloratadine in intermittent allergic rhinitis: a GA²LEN study. *Allergy* 2009;64:1516–1523.
- Fantin S, Maspero J, Bisbal C, Agache I, Donado E, Borja J, Mola O, Izquierdo I, international Rupatadine study group: A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. *Allergy* 2008;63:924–931.