Comparative effect of beclomethasone dipropionate and cetirizine on acoustic rhinometry parameters in children with perennial allergic rhinitis: a randomized controlled trial[§]

Running title: Beclomethasone versus cetirizine in PAR

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0263

[§]ClinicalTrials.gov ID: NCT02646904

Abstract

Background: The effect of intranasal corticosteroids and oral antihistamines on acoustic rhinometry parameters was not directly compared in previous studies.

Objectives: The primary aim was to compare the effect of 21-day treatment with nasal beclomethasone dipropionate (nBDP) versus cetirizine (CTZ) on nasal patency measured by acoustic rhinometry in children with PAR. Comparing their effect on nasal cytology, symptom severity, sleep quality and quality of life was the secondary aim.

Methods: In this 21-day, open-label, randomized controlled study, 34 PAR children (6–14 years) with Total 5 Symptom Score (T5SS) ≥5 received nBDP 100 μg per nostril twice daily or CTZ 10 mg tablets once daily. Effect measures were the least square mean changes (LSmc) in nasal volume and Minimal Cross-sectional Area (MCA), nasal cytology, T5SS, Pittsburgh Sleep Quality Index (PSQI) and Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ).

Results: After 21 days, nBDP improved nasal volume and MCA more than CTZ (LSmc 2.21 cm^3 *vs* 0.20 cm^3, p=0.013 and LSmc 0.63 cm^2 *vs* 0.13 cm^2, p=0.002, respectively). In the nBDP group, with respect to the CTZ group, larger improvement was found in: eosinophil (LSmc -1.10 *vs* -0.40, p=0.031) and neutrophil (LSmc -0.97 *vs* -0.17, p=0.010) classes, T5SS (LSmc -5.63 *vs* -3.54, p=0.008), PSQI (LSmc -1.30 *vs* -0.19, p=0.025) and PRQLQ total scores (LSmc -1.15 *vs* -0.69, p=0.031).

Conclusions: In children with PAR, nBDP is more effective than CTZ in improving nasal patency measured by acoustic rhinometry, with associated beneficial effects on nasal cytology, symptoms, sleep quality and quality of life.

Key words: Acoustic rhinometry. Allergic rhinitis. Beclomethasone dipropionate. Cetirizine. Children. Nasal patency.

doi: 10.18176/jiaci.0263

Resumen

Antecedentes: No hay estudios previos en los que se comparan los efectos sobre la rinometría acústica de los corticoides intranasales y los antihistamínicos orales.

Objetivos: El objetivo principal fue comparar los efectos de un tratamiento de 21 días con dipropionato de beclometasona (nBDP) frente a ceterizina (CTZ) sobre la obstrucción nasal medida con rinometría acústica en niños con rinitis alérgica perenne (PAR). Los objetivos secundarios incluyen los efectos sobre la citología nasal, la gravedad de los síntomas, la calidad del sueño y la calidad de vida.

Métodos: Estudio abierto, aleatorizado y controlado, de 21 días de duración. Se incluyeron 34 niños con PAR (6-14 años) con una puntuación de síntomas ≥5 (T5SS) que recibieron 100 µg de nBDP por fosa nasal dos veces al día o CTZ 10 mg una vez al día. Se realizaron las siguientes mediciones: cambios en los mínimos cuadrados (LSmc) del volumen nasal, del área transversa mínima (MCA), de la citología nasal, el T5SS, índice de calidad del sueño (PSQI) y el cuestionario de calidad de vida pediátrico (PRQLQ).

Resultados: después de 21 días, los tratados con nBDP mejoraron el volumen nasal y el MCA más que los tratados con CTZ (LSmc 2,21 cm^3 *vs* 0.20 cm^3, p=0,013 and LSmc 0,63 cm^2 *vs* 0,13 cm^2, p=0,002, respectivamente). En el grupo tratado con nBDP, con respecto a los tratados con CTZ tuvieron una mayor mejoría en la disminución de clases de eosinófilos (LSmc -1,10 *vs* -0,40, p=0,031) y neutrófilos (LSmc -0,97 *vs* -0,17, p=0,010), en el T5SS (LSmc -5,63 *vs* -3,54, p=0,008), PSQI (LSmc -1,30 *vs* -0,19, p=0,025) y en la puntuación total de PRQLQ (LSmc -1,15 *vs* -0,69, p=0,031).

Conclusiones: en niños con PAR, la nBDP es más efectiva que la CTZ en mejorar la obstrucción nasal medida por rinometría acústica, con los beneficios asociados sobre citología nasal, síntomas, calidad de sueño y calidad de vida.

Palabras clave: Rinometría acústica. Rinitis alérgica. Dipropionato de beclometasona. Ceterizina. Niños. Obstrucción nasal.

Background

Allergic rhinitis (AR) is the most common form of rhinitis in childhood, characterized by at least two symptoms among nasal itching, sneezing, rhinorrhea, and nasal congestion [1]. In particular, nasal congestion, defined as the discomfort experienced during breathing due to decreased nasal patency, is recognized as one of the most bothersome symptoms [2,3].

Nasal patency can be evaluated subjectively, through scales for symptom severity [4–6], or objectively, through different clinical measures [7]. Among them, acoustic rhinometry is a non-invasive tool validated to measure nasal cavity area and volume [8]. Indeed, in children volume parameters measured in the anterior part of the nose have been shown to be sensitive for change in nasal patency due to changes in mucosal swell after nasal provocation test [9] and after decongestion [10]. Nasal cytology (NC) also provides objective evaluation of the mucosal inflammation, providing insights into the efficacy of therapeutic interventions [11,12].

There is strong evidence about the efficacy of intranasal corticosteroids (INSs) in patients with perennial AR (PAR) [13]; in particular, nasal beclomethasone dipropionate (nBDP) has been shown to be effective both in reducing eosinophils and lymphocytes in nasal mucosa and in decreasing nasal symptoms [14]. For the same condition, use of oral antihistamines was conditionally recommended [13]; in particular, cetirizine (CTZ) showed good effectiveness in improving symptomatology [15].

Previous clinical studies in PAR children demonstrated the efficacy of INSs and oral antihistamines in improving acoustic rhinometry parameters and other subjective outcomes [16,17]. However, these outcomes were evaluated only through independent intragroup analyses or treatment comparisons versus placebo, the aforementioned studies lacking in direct comparison between the two active treatments. Moreover, the previous studies used

doi: 10.18176/jiaci.0263

different methodologies and different therapeutic interventions, and a comprehensive evaluation of different objective and subjective outcomes has not been fully accomplished.

The primary aim of the present study was to assess, in children with PAR, the effect of nBDP in comparison with CTZ on nasal patency measured by acoustic rhinometry. The secondary aim was to compare the effect of nBDP and CTZ on other objective (nasal cytology) and subjective (nasal symptom severity, sleep quality, quality of life) parameters.

Materials and Methods

Study design

This single-centre, open-label, randomized controlled study was approved by the local Institutional Ethics Committee (Palermo 1, Italy, Approval Number: 09/2015), and informed consent was obtained from all parents before study entry. The study was conducted in compliance with Good Clinical Practice and in accordance with the Declaration of Helsinki. The approved study was registered on the central registration system ClinicalTrials.gov (ID: NCT02646904).

Participants

One hundred twenty-eight children with PAR, aged 6-14 years, were assessed for eligibility at the pediatric allergy outpatient clinic of the IBIM (CNR, Palermo, Italy), from May 2016 through July 2017. The inclusion criteria were: (1) age 6–14 years; (2) clinical history of PAR in the last year, according to ARIA guidelines [18]; (3) allergic sensitization to *Dermatophagoides pteronyssinus*, defined upon a positive skin prick test (SPT) response (wheal ≥3 mm larger than the negative control test, Stallergenes, Milan, Italy) after 15 min [19]; (4) total five symptom score (T5SS) ≥5 (rhinorrhea, nasal obstruction, nasal itching,

sneezing, eye itching) [4] in the last week. The exclusion criteria were: (1) positive SPT to seasonal allergens and other perennial allergens; (2) medical diagnosis of nasal anatomic defects (i.e., septum deviation) or nasal polyp disease; (3) doctor diagnosis of asthma according to GINA guidelines [http://ginasthma.org]; (4) upper o lower respiratory tract infection in the last 2 weeks; (5) use of oral antihistamines, decongestants, leukotriene antagonists, systemic/topical antibiotics or corticosteroids in the last 4 weeks; (6) ongoing allergen immunotherapy; (7) active smoking. In addition, patients with compliance rate estimated at less than 80% were excluded.

Interventions

According to a computer-generated randomization sequence (1:1 allocation) unknown to the physicians, the sixty-eight eligible patients were assigned to one of two 21-day treatments: thirty-four children received nBDP twice daily 100 µg per nostril (beclomethasone dipropionate, Rinoclenil® nasal spray suspension, CHIESI Farmaceutici S.p.A., Parma, Italy); thirty-four children received once daily 10 mg CTZ (oral tablets 10 mg). Both nBDP and CTZ were provided by CHIESI Farmaceutici S.p.A. (Parma, Italy). All patients and their caregivers were instructed about nasal spray suspension usage through a brief demonstration.

Outcomes

The primary outcome was the change from baseline to 21 days of treatment in acoustic rhinometry parameters, namely nasal volume and Minimal Cross-sectional Area (MCA). Acoustic rhinometry was carried out using the device model Acoustic Rhinometer A1 (GM Instruments, Scotland) and the accompanying software according to the manufacturer's instructions. All measurements were performed by the same pediatrician

doi: 10.18176/jiaci.0263

(VM). The device was calibrated prior to each measurement. Following current recommendations, children were tested after twenty minutes of acclimatization in the test room [20]. Special soft nosepieces for children were used. If necessary, ultrasound gel was used to prevent acoustic leakage. No nasal decongestant was used. The mean values of three acceptable measurements with a standard deviation less than 5% were used for calculations. The values of special interest were the nasal volume (cm^3) from the first 5 *cm* from the nostril, and the MCA (cm^2). Total values were calculated by adding each nostril value.

The secondary outcomes were the changes from baseline to 21 days of treatment in nasal cytology classes and several subjective scales, as detailed below.

Nasal cytology was performed by using a small plastic curette (Rhinoprobe^{TM}) in anterior rhinoscopy, following recent recommendations [21]. Neutrophils and eosinophils were classified as: 0=none; 1=few scattered cells; 2=moderate number; 3=large clumps [21].

The Total 5 Symptom Score (T5SS) is a subjective scoring system for determination of symptom severity based on five domains: rhinorrhea, nasal obstruction, nasal itching, sneezing and eye itching. Each symptom is scored on a 4-point scale from 0 to 3. Total score is calculated by adding the scores for all the 5 domains, and ranges from 0 (not troubled) to 15 (extremely troubled) [4].

The Pittsburgh Sleep Quality Index (PSQI) is a self-administered questionnaire, 4-week recall, including 19 questions in 7 domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications and daytime dysfunction. Each domain is scored from 0 to 3, so that the total score ranges from 0 (not troubled) to 21 (extremely troubled) [22].

The Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is a self-administered questionnaire, 4-week recall, for assessing physical, emotional and social problems in subject with AR. It includes 23 items in five domains: nose symptoms, eye

doi: 10.18176/jiaci.0263

symptoms, practical problems, activity limitation and other symptoms. Each domain is scored on a 7-point scale (from 0=not troubled to 6=extremely troubled). The overall score is obtained from the mean score of all items [23].

Assessments

Detailed medical history was obtained by well-trained physicians (VM, GF, SLG), investigating clinical symptoms, host factors and environmental exposures. In particular, information about current (last 12 months) exposure to passive smoke, mold, pets and traffic was derived from a standardized questionnaire administered to parents [24].

The study involved three visits: screening (visit 1), randomization (visit 2, baseline) and final assessment (visit 3, day 21+1). At visit 1, patients were assessed for eligibility and recruited if they met the inclusion criteria. Typically, 1 to 7 days elapsed from enrolment to randomization. Physical examination and variable assessment was performed at each visit. When necessary, questionnaires were completed under the supervision of one of the researchers (L.M.) during the visits.

Patients and caregivers were instructed to record on a diary card, daily throughout the treatment period, the occurrence and severity of side effects, as well as information about severity of nasal symptoms, use of concomitant medications and treatment adherence. Adherent patients were considered those who had taken at least ≥80% of the scheduled treatment.

Sample size

The sample size of the present study was based on pilot data from a previous study [17] investigating the effect of topical nasal steroid on the nasal volume in children and adolescents with PAR. In the aforementioned study, the nasal volume increased from a

baseline mean value of 8.2 cm^3 to 9.3 cm^3 (SD approximately equal to 1.5). Detecting a similar change with an 80% statistical power and a 5% significance level would have required a sample size of 30 children for each treatment group. To account for a 10% to 15% hypothesized dropout rate, the sample size was therefore established at 34 patients per group.

Statistical analysis

Baseline characteristics of children were compared between nBDP and CTZ groups through t-test for two means (quantitative variables) and Chi-squared test for percentages (categorical variables). Correlations between acoustic rhinometry parameters and other objective and subjective scores were evaluated through Kendall's Tau test.

The treatment effect was assessed on children who completed the study. For the primary outcomes, an exploratory analysis was performed through the Wilcoxon test for assessing the change from baseline in the two treatment groups. Both for the variables of primary and secondary interest, the mean change from baseline in the two treatment groups was compared using linear regression models adjusted for age, weight, current (last 12 months) exposure to smoke, mold and pets (cat and/or dog), traffic density and the baseline value of the variable of interest. Comparisons were performed in term of least square mean change (LSmc) (*R* package *emmeans*).

P-values lower than 0.05 were considered to indicate a statistically significant effect. Statistical analyses were performed through R version 3.4.2.

Results

Descriptive statistics. Out of the 128 screened patients, 60 were excluded due to violation of entry criteria or detection of exclusion criteria (Fig. 1). Overall, out of the 68 randomized children, 65 (96%) completed the study. In particular, out of the 34 randomized

patients in CTZ, 31 completed the study: 1 patient (3%) withdrew the consent, while 2 children (6%) were lost to follow-up (change of residence). All the 34 randomized patients in nBDP completed the study. Demographic characteristics and current (last 12 months) environmental exposures were similar between the two groups at baseline (Table 1). Baseline values of the variables of primary and secondary interest were also comparable (Table 2).

For both groups at both visits eosinophils classes were negatively correlated with volume (Kendall's Tau=-0.21, p=0.003) and MCA (Kendall's Tau=-0.14, p=0.040) (Fig. 2), while correlations between acoustic rhinometry parameters and all the subjective scores were not statistically significant.

For children who completed the study, the level of adherence was 100% in both the treatment groups, no adverse events (AEs) were observed and no concomitant medication use was reported.

Primary outcome. The exploratory analysis showed that volume values increased significantly after 21 days in the nBDP group (p=0.033), while the change was not significant in the CTZ group (p=0.900) (Fig. 3, top panels). Similarly, MCA values increased significantly in the nBDP group (p=0.045), while the change was not significant in the CTZ group (p=0.840) (Fig. 3, bottom panels). After adjusting for the confounders, nBDP was found to improve the nasal volume more than CTZ (LSmc 2.21 cm^3 *vs* 0.20 cm^3, p=0.013) (Table 3). Similarly, nBDP improved the MCA more than CTZ (LSmc 0.63 cm^2 *vs* 0.13 cm^2, p=0.002).

Secondary outcomes. In the nBDP group, with respect to the CTZ group, larger improvement in: eosinophil (LSmc -1.10 *vs* -0.40, p=0.031) and neutrophil (LSmc -0.97 *vs* -0.17, p=0.010) classes, T5SS total score (LSmc -5.63 *vs* -3.54, p=0.008), PSQI total score (LSmc -1.30 *vs* -0.19, p=0.025) and PRQLQ total score (LSmc -1.15 *vs* -0.69, p=0.031) (Table 3).

doi: 10.18176/jiaci.0263

Discussion

The present study demonstrates the greater efficacy of a 21-day treatment with nBDP, in comparison with oral CTZ, on improving nasal patency measured by acoustic rhinometry in children with PAR.

Despite its feasibility and non-invasiveness, acoustic rhinometry is not extensively used in paediatric age. This may be ascribed to the reported weak correlation with self-reported nasal congestion [25,26], which was also shown in the present study. To date, only a limited number of studies, characterized by different study designs and different INSs treatment, evaluated acoustic rhinometry among the outcomes in PAR children [16,17,27]. Since none of these studies evaluated the effect of nBDP treatment, the findings of the present study can be only partially compared with previous results.

This study showed significant improvements in nasal volume from the first 5 cm from the nostril and in MCA, representative of the anti-inflammatory effect of nBDP treatment. The reported effects were expressed in terms of least square mean changes. The least square means simply represent the predicted means of the outcomes in a hypothetical population of patients with balanced (uniform) distribution of the variables included in the model, specifically age, weight, current exposure to smoke, mold and dog/cat, traffic density and baseline value of the variable of interest. As a result, the reported least square mean changes are expressed in the same unit of measurement as the outcomes, and therefore have a real, direct clinical meaning. As highlighted by Straszek et al. [10], sensitivity of volume parameters to changes in nasal patency has to be ascribed to the change in mucosal swell. However, somewhat discordant findings arose from previous studies. In particular, a similar result was observed by Wandalsen et al. [17], where the authors evaluated the effect of a 21-day course of mometasone furoate 100 µg once a day, demonstrating a significant increase in all the investigated acoustic rhinometry parameters, as well as a decrease in the nasal

symptom score. On the contrary, de Andrade et al. did not observe significant differences in nasal cavity volume after a 6-week course of fluticasone propionate [27].

In addition, nBDP was found to improve nasal volume and MCA to a greater extent than CTZ. Even though assessed in previous placebo-controlled study in children with PAR [16,28], INSs and anti-histamines effects on nasal patency had not been explicitly compared. In the present study, the greater effect of nBDP in comparison with CTZ was also corroborated by the higher reduction in nasal inflammatory cells, such as eosinophil and neutrophil counts. This reinforces previous results of a placebo-controlled study [29] which did not include anti-histamine arms, providing more evidence about the efficacy of nBDP in decreasing the chronic inflammation of the upper airways in patients mono-sensitized to the perennial allergen *Dermatophagoides pteronyssinus*.

The current study also integrates previous findings about the efficacy of nBDP in improving symptom severity in children [30] and adolescents [31] with PAR, as well as quality of life [31] and sleep quality [32,33]. More in detail, nBDP was found to improve T5SS, PSQI and PRQLQ total scores largely than CTZ. Noteworthy, none of the available studies investigating the effect of different treatments on nasal patency performed a comprehensive approach including subjective outcomes such as sleep quality and quality of life [16,17,27]. Indeed, the importance of assessing these parameters within the clinical setting has been emphasized in view of a holistic approach to be performed also in pediatric age. In fact, it is well known that symptoms of PAR can negatively affect children's activities and sleep quality, leading to daytime somnolence and fatigue [34].

The main novelty of this study is the comparative investigation of the effect of topic nBDP and oral CTZ on nasal patency in children with PAR, evaluated through acoustic rhinometry and other objective and subjective outcomes. In fact, the higher effect of nBDP in comparison with CTZ was supported by concomitant improvements observed in nasal

doi: 10.18176/jiaci.0263

cytology, nasal symptom severity, quality of life and sleep quality scores. Such comprehensive assessment may be useful in the clinical management of children with PAR.

Even if three patients dropped out in CTZ (31 completed the study), this has not influenced the desired power of the study, since actually 30 patients per group would have been enough, as detailed in the sample size section. Another positive aspect is the high compliance with daily treatment; in fact, the level of adherence was 100% in both the treatment groups, thanks to close telephone follow-up by well-trained investigators. nBDP treatment was also well tolerated and no AEs were observed.

The main limitation of the present study is non-blindness of patients and investigators. However, this aspect may have not affected the results due to the objective nature of the primary outcomes (and concordant results found for the secondary outcomes). Another possible limitation is the absence of objective evaluation of drug safety; this was not performed since a recent study on nasal treatment with nBDP failed to show significant systemic effect in treated children with PAR [35]. The reported lack of hypothalamus-pituitary-adrenal (HPA) axis suppression may be attributable to the low systemic bioavailability of nBDP, due to the low absorption through respiratory and digestive mucus membranes [36].

Conclusions

The current study demonstrated the greater effect of nBDP in comparison with CTZ on nasal permeability measured by acoustic rhinometry in children with perennial AR. Similarly, a greater anti-inflammatory effect of nBDP resulted on a reduction in nasal inflammatory cell counts. Moreover, nBDP resulted to be effective in reducing the subjective burden suffered by patients, with beneficial effects on symptom severity, quality of life and quality of sleep.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Table 1. Characteristics of children at baseline.

	CTZ (n=34)	nBDP (n=34)	P-value[§]
Anthropometric characteristics			
Gender			0.800
Male	23 (68%)	21 (62%)	
Female	11 (32%)	13 (38%)	
Age, *years*	9.47 (2.36)	10.06 (2.35)	0.307
Weight, *kg*	36.94 (11.2)	37.56 (14.03)	0.842
Height, *cm*	139 (14.47)	139.59 (16.37)	0.877
AR duration, years			0.487
1-3	16 (47%)	14 (41%)	
4-5	5 (15%)	9 (28%)	
>5	13 (38%)	11 (31%)	
[§§]Current environmental exposures			
Passive smoke	8 (24%)	8 (24%)	1.000
Mold	8 (24%)	5 (15%)	0.537
Dog	9 (26%)	6 (18%)	0.559
Cat	3 (9%)	3 (9%)	1.000
Traffic density			0.576
Absent	4 (12%)	6 (18%)	
Low	10 (29%)	13 (38%)	
Moderate	7 (21%)	7 (21%)	
High	13 (38%)	8 (24%)	

Data are presented as mean (SD) for quantitative variables, n (%) for categorical variables. CTZ: cetirizine; nBDP: nasal beclomethasone dipropionate; AR: allergic rhinitis. [§]t-test for quantitative variables, Chi-squared test for categorical variables. [§§]Last 12 months.

Table 2. Variables of primary and secondary interest at baseline.

	CTZ (n=34)	nBDP (n=34)	P-value[§]
Acoustic rhinometry			
Volume, cm^3	5.77 (1.51)	5.91 (1.49)	0.703
MCA, cm^2	0.68 (0.32)	0.69 (0.25)	0.893
Nasal cytology			
Eosinophil classes			0.255
None (score=0)	10 (31%)	16 (50%)	
Few scattered cells (score=1)	8 (25%)	5 (16%)	
Moderate number (score=2)	12 (38%)	7 (22%)	
Large clumps (score=3)	2 (6%)	4 (12%)	
Neutrophil classes			0.223
None (score=0)	15 (47%)	21 (66%)	
Few scattered cells (score=1)	2 (6%)	2 (6%)	
Moderate number (score=2)	4 (12%)	5 (16%)	
Large clumps (score=3)	11 (34%)	4 (12%)	
T5SS total score	8.56 (2.7)	8.21 (2.56)	0.591
PSQI total score	7.28 (1.89)	6.79 (3.13)	0.446
PRQLQ total score	3 (1.21)	2.74 (1.13)	0.383

Data are presented as mean (SD) for quantitative variables, n (%) for categorical variables. CTZ: cetirizine; nBDP: nasal beclomethasone dipropionate; MCA: minimal cross-sectional area; T5SS: total five symptom score; PSQI: Pittsburgh sleep quality index; PRQLQ: Paediatric Rhinoconjunctivitis Quality of Life Questionnaire. [§]t-test for quantitative variables, Chi-squared test for categorical variables.

Table 3. Mean change from baseline in variables of primary and secondary interest over the treatment period.

	CTZ (n=31)	nBDP (n=34)
Volume, cm^3		
LS mean change (p-value)	0.10 (0.810)	1.11 (**0.039**)
LS mean change difference (p-value)		1.01 (**0.013**)
MCA, cm^2		
LS mean change (p-value)	0.06 (0.441)	0.31 (**0.002**)
LS mean change difference (p-value)		0.25 (**0.002**)
Eosinophil classes		
LS mean change (p-value)	-0.40 (0.202)	-1.10 (**0.008**)
LS mean change difference (p-value)		-0.70 (**0.031**)
Neutrophil classes		
LS mean change (p-value)	-0.17 (0.565)	-0.97 (**0.016**)
LS mean change difference (p-value)		-0.80 (**0.010**)
T5SS total score		
LS mean change (p-value)	-3.54 (**<0.001**)	-5.63 (**<0.001**)
LS mean change difference (p-value)		-2.09 (**0.008**)
PSQI total score		
LS mean change (p-value)	-0.19 (0.706)	-1.30 (**0.050**)
LS mean change difference (p-value)		-1.11 (**0.025**)
PRQLQ total score		
LS mean change (p-value)	-0.69 (**0.003**)	-1.15 (**<0.001**)
LS mean change difference (p-value)		-0.46 (**0.031**)

Significant changes are shown in bold. LS: Least Square; CTZ: cetirizine; nBDP: nasal beclomethasone dipropionate; MCA: minimal cross-sectional area; T5SS: total five symptom score; PSQI: Pittsburgh sleep quality index; PRQLQ: Paediatric Rhinoconjunctivitis Quality of Life Questionnaire. Models were adjusted for age, weight, current exposure to smoke, mold and dog/cat, traffic density and baseline value of the variable of interest.

Figure Legends

Figure 1. Study flowchart. ITT: intention-to-treat. CTZ: cetirizine; nBDP: nasal beclomethasone dipropionate.

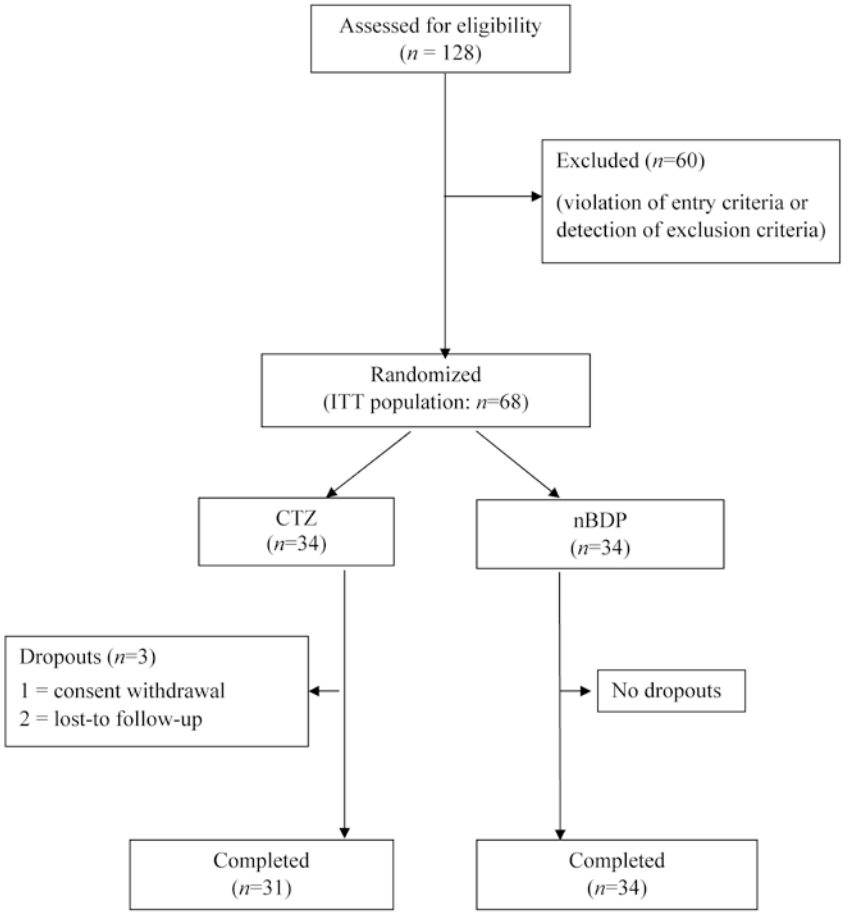

Figure 2. Correlations between acoustic rhinometry (Volume, a; MCA, b) and eosinophils classes in CTZ and nBDP groups at T0 and T1 visits. For both groups at both visits eosinophils classes were negatively correlated with volume (Kendall's Tau=-0.21, p=0.003) and MCA (Kendall's Tau=-0.14, p=0.040).

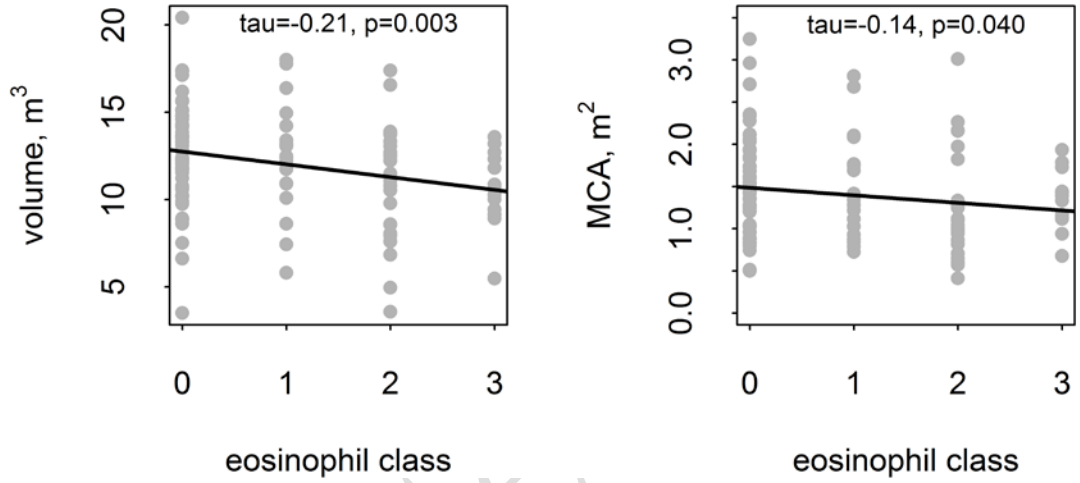

Figure 3. Volume and MCA values at T0 and at T1 for the two study groups. CTZ: cetirizine; nBDP: nasal beclomethasone dipropionate. After 21 days: volume values increased significantly in the nBDP group (p=0.033) *vs* not significant change in the CTZ group (p=0.900) (top panels); MCA values increased significantly in the nBDP group (p=0.045) *vs* not significant change in the CTZ group (p=0.840) (bottom panels).