

ORIGINAL ARTICLE

Effects of mometasone furoate on the quality of life: a randomized placebo-controlled trial in persistent allergic rhinitis and intermittent asthma using the Rhinasthma questionnaire

I. Baiardini¹, E. Villa¹, A. Rogkakou¹, S. Pellegrini¹, M. Bacic¹, E. Compalati¹, F. Braido¹, C. Le Grazie², G. W. Canonica¹ and G. Passalacqua¹

¹Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genoa, Italy and ²Medical Division, Schering-Plough Spa, Milan, Italy

Clinical & Experimental Allergy

Summary

Background Allergic rhinitis, especially when persistent (PER) and associated with asthma heavily impairs patients' quality of life (QoL).

Objective This study assessed the effect of mometasone furoate nasal spray (MFNS) on the QoL of patients with PER and asthma, using the Rhinasthma questionnaire (EUDRACT n. 2007-004683-45).

Methods Patients with moderate/severe PER and intermittent asthma were randomized to MFNS (alcohol-free) 200 µg/day or placebo for 28 days. Rhinasthma was completed at baseline and at weeks 2 and 4. The total five symptom score (T5SS) for rhinitis, the asthma symptom score and the sum of the two [global symptoms score (GSS)] were recorded daily. The primary outcome was the change in the Rhinasthma global summary (GS) at the end of treatment. Secondary end-points were (a) the change from baseline to end of treatment of each Rhinasthma factor: upper airways (UAs), lower airways (LAs) and respiratory allergy impact; (b) the change from baseline to end of treatment of the T5SS and of the GSS and (c) the use of rescue medication.

Results Fifty-two adults were randomized. Compared with placebo, MFNS produced a significant change in the Rhinasthma GS (−10.4 vs. 0.4; $P < 0.01$). MFNS also achieved a significant improvement of the UA (−16.6 vs. 0.1; $P < 0.001$), LA (−10.8 vs. 1.1; $P < 0.001$) and GSS (−6.7 vs. −3.1; $P = 0.019$). The change of the T5SS was greater in the MFNS group but did not reach statistical significance.

Conclusion In patients with PER rhinitis and intermittent asthma, MFNS improves the QoL and the burden of respiratory symptoms. Treating rhinitis may affect the asthma-related QoL.

Keywords intermittent asthma, mometasone furoate nasal spray, persistent rhinitis, quality of life, respiratory allergy

Submitted 23 July 2010; revised 14 September 2010; accepted 18 October 2010

Correspondence:

Giovanni Passalacqua, Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Padiglione Maragliano, Lgo R. Benzi 10, 16132 Genoa, Italy.
E-mail: passalacqua@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]. AR has been classified as seasonal or perennial, according to the responsible allergen, but this classification does not consider the possible overlapping exposure to different allergens, the underlying pathophysiology, and the duration of symptoms. For these reasons a new classification has been proposed, defining rhinitis as intermittent or persistent (PER), according to the duration, and as mild or moderate/

severe, according to the severity of symptoms and the impairment of daily activities and sleep [1]. This classification proved adherent to the clinical reality [2, 3] and, therefore, it has been widely accepted.

AR is not a life-threatening condition, but it affects the health-related quality of life (HRQoL) of patients, impairs their work [4] and school performance [5] and leads to relevant expenditures [6]. The impact of AR on HRQoL is well-established [7], and it is definitely greater for PER [8]. In addition, PER is often associated with asthma [9], and represents an independent risk factor for the development of asthma itself [10]. This results in substantial cost

increase and additional impact on the HRQoL. Thus, it has become progressively clear that in evaluating the effectiveness of a treatment for AR, HRQoL must be included within outcomes, in parallel to symptoms; the relevance of HRQoL evaluation in clinical, research and regulatory processes is now well recognized [11, 12]. There are several HRQoL questionnaires for respiratory allergy, but they are specifically designed for rhinitis [13] or asthma [14] separately. A specific questionnaire named Rhinasthma, which measures the impact of both diseases on HRQoL, has been developed and validated [15].

As mentioned above, rhinitis is an inflammatory disorder of the nasal mucosa, where numerous cells, cytokines and adhesion receptors are involved. When the allergen exposure is long-lasting, as happens in PER, the inflammation becomes chronic and more difficult to treat. This is the reason why nasal corticosteroids are overall more effective than antihistamines in controlling nasal symptoms [16]. Mometasone furoate nasal spray (MFNS) has been shown to be effective in PER and to improve the quality of life (QoL) of patients with AR [17]. Nonetheless, no study has evaluated the efficacy of MFNS on concomitant rhinitis and asthma symptoms, and how the improvement of symptoms is perceived by the patient. On this basis, we designed an exploratory clinical trial to evaluate the effects of MFNS in PER associated with intermittent asthma, using the HRQoL for the associated conditions as primary outcome.

Methods

Study design

This was a single-centre, randomized, double-blind, placebo-controlled, two-parallel group trial. After a 1-week run-in period with placebo, the patients were randomized (Visit 2) to receive either MFNS or placebo during a 4-week double-blind phase. The subjects attended control visits at week 2 (Visit 3) and at the end of the treatment period (week 4, Visit 4). A ± 1 -day window was allowed for the planned visits. The HRQoL was assessed at baseline and at 2 and 4 weeks, whereas symptoms of asthma and rhinitis were recorded throughout the study on a diary card. Primary outcome was the change vs. placebo in the global summary (GS) of the Rhinasthma questionnaire. The occurrence of adverse events was assessed as well throughout the study period. The study was conducted in January–February, to avoid the confounding effect of concomitant sensitizations, if any. The study was approved by the local Ethics Committee, and all patients signed an informed consent before inclusion (EUDRACT n. 2007-004683-45).

Patients

Adult subjects of both sexes, suffering from moderate/severe PER [1] and mild intermittent asthma [18] were

enrolled. Inclusion criteria were: (a) clinical history of PER in the last 2 years; (b) clinical history of mild intermittent asthma in the last 2 years; (c) actual asthma (symptoms during the last 4 weeks); (d) sensitization to at least house dust mite, assessed by skin prick test or CAP-RAST; (e) a total five symptom score (T5SS) > 6 in at least 4 days of the run-in. Patients with PER asthma, chronic obstructive pulmonary disease, systemic immunological disorders or malignancies were excluded, as were subjects with mechanical abnormalities of the nose (polyps, septal deviation, turbinate hypertrophy). Other exclusion criteria were chronic systemic corticosteroid therapy or allergen-specific immunotherapy. Pregnant or breastfeeding women were excluded as well.

Interventions

The investigated drug was an alcohol-free preparation of MFNS. The dose was 100 mcg per nostril once daily in the morning, administered by a metered-dose, manual pump spray. The placebo was the same vehicle used for the medication, and it was indistinguishable in aspect, colour and flavour from the active treatment. The blinding was granted by a computer-generated randomization list, and the active and placebo preparations were delivered pre-packed by the manufacturer to the centre. At the screening visit, each nasal spray device was primed until a fine spray was obtained. The investigator performed this priming procedure while instructing the subject on the correct use of the nasal spray. The correct use of the spray was reviewed at the subsequent visits.

No other medication, either topical or systemic, was allowed during the study. Patients were provided with rescue medications to be used on demand, i.e. topical cromolyn (one spray per nostril three times a day), and inhaled salbutamol (two puffs on demand). Unused and/or partially used drugs had to be returned at each visit. An accurate accounting of the dispensing and return of treatment and rescue medications was maintained by a member of the site staff in a drug accountability log.

Rhinasthma questionnaire

HRQoL was assessed using the Rhinasthma, a specific QoL questionnaire which measures the impact of rhinitis and asthma on daily life [15]. The questionnaire had to be completed by patients at Visit 2 (end of the run-in, before randomization), and after 2 and 4 weeks. The Rhinasthma is composed of 30 items, grouped into three factors [respiratory allergy impact (RAI), upper airways (UAs) and lower airways (LAs)]. These items are also pooled together providing a GS. Each item is rated on a Likert scale with multiple options (1 = not at all, 5 = very much), indicating how troublesome the problem was during the past 2 weeks. Answers to the Rhinasthma items are then

converted into a score from 0 to 100. A higher score indicates a worse HRQoL.

Symptom scores and diary card

The patients reported on a diary the presence and intensity of symptoms in the morning before dosing and in the evening. The T5SS concerned the UAs, and included sneezing, rhinorrhea, nasal itching, nasal obstruction and itchy eyes. Each symptom was scored from 0 (absent) to 3 (severe), so that the maximum possible score was 15 points. Asthma symptoms included wheezing, cough, dyspnoea, night awakenings and chest tightness, and were also scored from 0 to 3 each. The sum of the T5SS and the asthma score provided a global symptom score (GSS). Daily T5SS and GSS were calculated averaging morning and evening T5SS and GSS, respectively. At inclusion, the patients had to have a T5SS > 6 for at least 4 days of the run-in. This was established to ensure that patients were symptomatic. Mean daily and weekly values of T5SS and GSS were calculated for statistical analysis. The number and percentage of subjects using rescue medications and the number of days of use of rescue medication were also recorded.

Statistical analysis

The primary efficacy variable was the change in the Rhinasthma GS from baseline to end-point after 28 days of treatment. Secondary efficacy variables were: (a) changes in the UAs, LAs and RAI from baseline to the end of the treatment, (b) changes in the T5SS and GSS from baseline to end of treatment and (c) the use of rescue medications in the post-randomization period.

The following populations were considered for analysis: intent to treat (ITT), defined as all randomized patients who received at least one dose of study medication and with at least one valid post-baseline assessment of the primary efficacy variable; per-protocol (PP), defined as all ITT patients without major protocol deviations; safety population: all randomized subjects who received at least one dose of study medication. Differences were tested using an ANCOVA model with treatment as factor and baseline value as covariate. The overall treatment effect was tested using an *F*-test at the two-sided 5% level of significance. A repeated measures ANOVA test was used for the analysis of the four scores of the Rhinasthma questionnaire and the daily scores of T5SS and GSS. A multivariate two-way ANOVA was used to evaluate the overall time effect. For the primary efficacy analysis missing data for the primary end-point (Rhinasthma GS) at the end of treatment were imputed with the Last Observation Carried Forward method. The same procedure was used for the other Rhinasthma scores and for the daily diary scores. The number of subjects using rescue medications was

analysed using the two-sided χ^2 test. A Wilcoxon test was used to compare the number of days of administration of the rescue medications.

The primary efficacy analysis was performed on the ITT and PP population. The secondary end-points were analysed on an ITT basis only. A total sample size of 46 subjects would have had 90% of power to detect a difference of 10 in the Rhinasthma GS, assuming a standard deviation of 10 and using a level of significance of 0.05 in two-sided testing. Considering a 20% dropout rate, the sample size was increased to $N = 56$.

Results

Fifty-seven patients were screened and 52 patients fulfilling the inclusion criteria were randomized. The patients' disposition is shown in Fig. 1. The ITT population consisted of 52 subjects, whereas the PP population included 47 patients. The two groups were homogeneous at baseline, and their characteristics are summarized in Table 1. Compliance was assessed by diary cards and was > 95% in the two groups in both the run-in and double-blind period.

The Rhinasthma GS displayed a significant reduction from baseline in the active group. The comparison of the adjusted means ($\pm$ SE) of change from baseline to end of treatment were -10.36 ± 1.98 (95% CI, -14.33 to -6.38 , $P < 0.001$) in the mometasone group and 0.43 ± 2.02 (95% CI, -3.62 to 4.49 , $P = 0.831$) in the placebo group. The difference between the adjusted means of the two groups was -10.79 (95% CI, -16.47 to -5.11), with a significant difference ($P < 0.001$). The GS reduction from baseline in the MFNS group was also significant at week 2 ($P < 0.001$), whereas no change from baseline was seen in the placebo group at week 2 or 4 (Fig. 2). In the PP population the difference between the adjusted means of the MFNS and the placebo group was -9.56 (95% CI -15.17 to -3.94) showing a significant difference in favour of MFNS ($P = 0.001$).

Significant differences were found also for the UA and LA components of Rhinasthma at weeks 2 and 4 vs. baseline and between groups, as shown in Fig. 3. On the other hand, the RAI displayed a small decrease from baseline at weeks 2 and 4 in both treatment groups, and the decrease at week 4 was slightly greater in the MFNS [-4.26 (95% CI, -8.62 to -0.09)] than in the placebo group [0.22 (95% CI, -4.22 to 4.66)], but no statistical significance was reached ($P = 0.156$).

The T5SS decreased from baseline at any time-point in both treatment groups. The extent of the decrease was higher in the MFNS group than in the placebo group, but no statistical significance was achieved vs. baseline and between groups (Fig. 4). For the GSS, a decrease from baseline was observed in both treatment groups, but the extent of the decrease was higher in the MFNS group. The

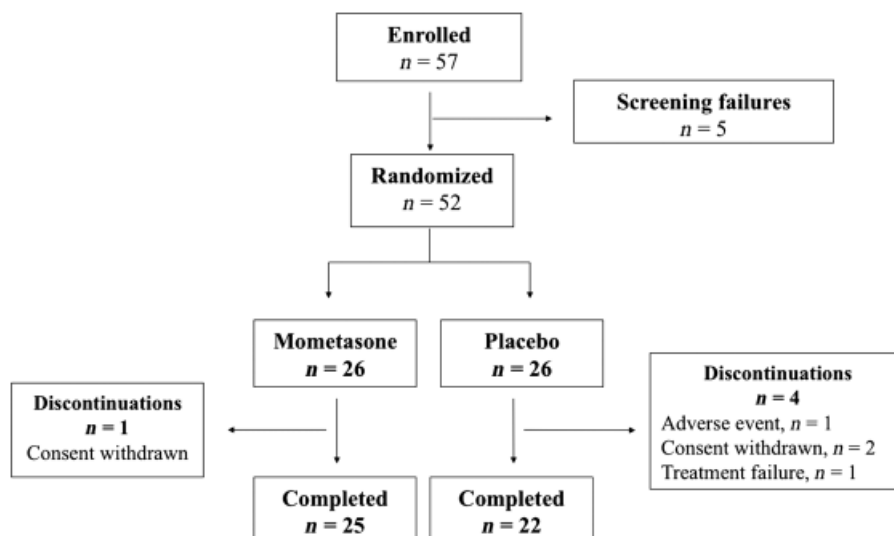


Fig. 1. Patients' disposition.

Table 1. Characteristics of the ITT population at baseline

	MFNS (N = 26)	Placebo (N = 25)
Gender, M/F	15/11	13/12
Age (years)		
Mean (SD)	40.5 (13.42)	43.0 (16.62)
Range	18–71	22–68
Duration of PER (years)		
Mean (SD)	8.93 (7.02)	13.34 (9.69)
Range	2.4–25	2–30
Duration of asthma (years)		
Mean (SD)	7.19 (7.25)	9.45 (9.66)
Range	2–25	1–30
Rhinasthma GS		
Mean (SD)	25.3 (10.3)	26.7 (18.9)
Range	1.7–46.7	4.2–73.3
Rhinasthma UAs		
Mean (SD)	35.4 (13.88)	33.7 (25.4)
Range	2.8–72.2	3.1–86.1
Rhinasthma LAs		
Mean (SD)	22.5 (9.88)	23.5 (18.3)
Range	0–44.2	0–67.3
Rhinasthma RAI		
Mean (SD)	19.8 (12.2)	24.8 (19.7)
Range	0–43.8	0–71.9
T5SS		
Mean (SD)	7.8 (1.4)	8.9 (1.8)
Range	6–11	6.7–13
GSS		
Mean (SD)	10.7 (2.6)	10.3 (2.7)
Range	7.6–16.1	7.2–16.4

MFNS, mometasone furoate nasal spray; ITT, intent to treat; PER, persistent; GS, global summary; UAs, upper airways; LAs, lower airways; RAI, respiratory allergy impact; T5SS, total five symptom score.

comparison between groups with the ANCOVA model showed that the adjusted means ($\pm$ SE) of change from baseline to end of treatment were -6.66 ± 1.02 (95% CI,

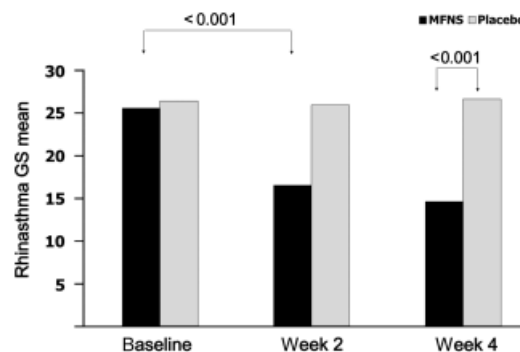


Fig. 2. Rhinasthma global summary at baseline, after 2 weeks and after 4 weeks. The significant differences are plotted above the bars.

-8.71 to -4.61 , $P < 0.001$) in the MFNS group and -3.12 ± 1.04 (95% CI, -5.21 to -1.02 , $P = 0.004$) in the placebo group. The difference between the adjusted means of the two groups was -3.54 (95% CI, -6.48 to -0.60), thus showing a statistically significant difference ($P = 0.019$) in favour of MFNS (Fig. 4). Of note, in the first week of treatment a significant time $\times$ treatment interaction was observed ($P = 0.018$) indicating that the two groups had different changes over time in the GSS, and the difference vs. baseline became significant in the active group since the first day of treatment (Fig. 5). There was no difference between MFNS and placebo group in the number of days with use of rescue medications (5.1 ± 7.98 vs. 9.5 ± 10.31 ; $P = 0.096$) or in the proportion of patients taking rescue medications during the treatment period (65.4% vs. 76.0%; $P = 0.406$). Nonetheless a progressive decrease of the proportion of patients using rescue medications was seen during the study only in the MFNS group (baseline 73.1%, week 1 46.2%, week 2 34.6%, week 3 44%, week 4 32%). The treatments were well-tolerated.

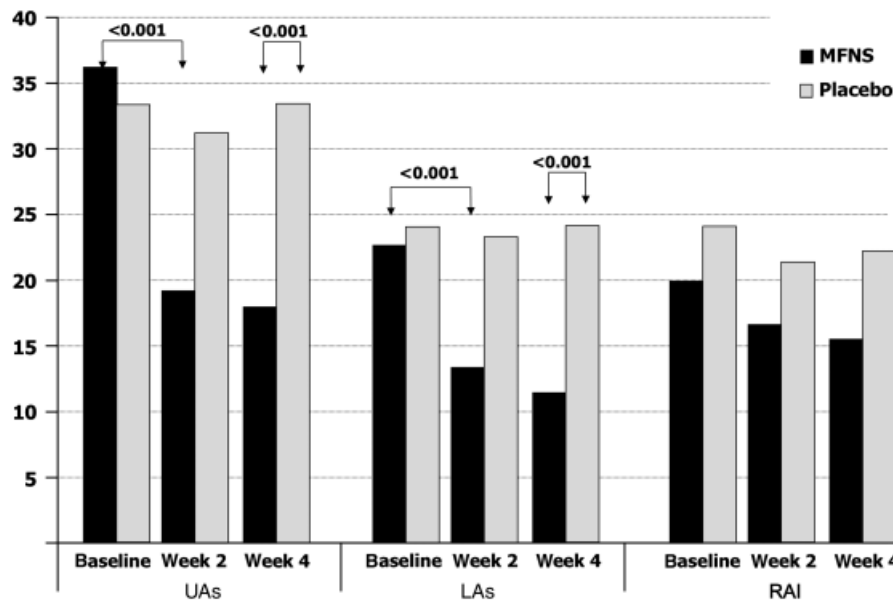


Fig. 3. Rhinasthma upper airways (UAs), lower airways (LAs) and respiratory allergy impact (RAI) components at baseline, after 2 weeks and after 4 weeks. The significant differences are plotted above the bars.

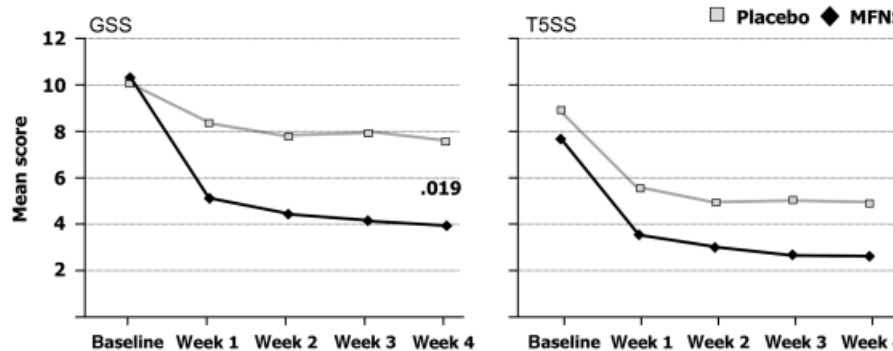


Fig. 4. Global symptom score (GSS, left) and total five symptom score (T5SS, right) at the different time-points.

Only one adverse event (severe rhinitis) was seen in one placebo patient who discontinued the study.

Discussion

In this clinical trial we found that MFNS significantly improved the global perception of HRQoL, and the improvement was significant also for the parameters exploring the LAs.

The treatment of AR relies on patient education, medications and immunotherapy [1]. Among medications, intranasal corticosteroids have the best efficacy in controlling symptoms, especially congestion [16], as they modulate the underlying inflammation at different steps. This is of special relevance in the PER forms of rhinitis, where obstruction is the most troublesome symptom, heavily affecting the patient's well-being. In general, when the efficacy of a drug, including nasal steroids, is

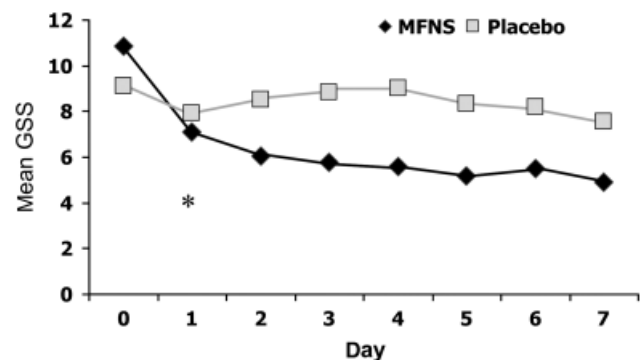


Fig. 5. Global symptom score during the first week of treatment. * $P = 0.013$, day 1 vs. day 0 in the active group.

evaluated, symptoms are chosen as the primary outcome. Nonetheless, the perception of the disease and of the impact of treatment by the patient is equally important. In fact, it is now recognized that HRQoL is an essential

parameter in clinical trials of drugs [11, 12, 19]. This is especially true when concomitant diseases are investigated at the same time, as happens for asthma and rhinitis. The recent recommendations for Patient Reported Outcomes assessment in clinical trials on allergy suggest, in evaluating HRQoL patients with rhinitis and comorbid asthma, the use of tools that take into account both diseases [20]. This is the reason the present study was designed with a HRQoL assessment as the primary outcome, and using a tool that is capable of appreciating the two components separately and in a GS. The main robustness of the study, in addition to the randomized double-blind design, was that all the enrolled patients had to be symptomatic, and to strictly fit the ARIA criteria for duration and severity of their AR. In addition, a sample size calculation based on the primary outcome was performed.

The main result of the trial was that MFNS significantly improved the global perception of HRQoL, as testified by the changes in the GS of the Rhinasthma. In addition, both the UA and LA components of the HRQoL were similarly improved. This finding is paralleled by the improvement in the global clinical score of symptoms (asthma + rhinitis) as early as day 1 of treatment, which confirms the fast onset of action of MFNS [21]. No significant changes have been detected in RAI: this may be explained taking into account the meaning of this factor. RAI includes some aspects strictly related to the disease management (i.e. necessity of medical controls, necessity of taking drugs, necessity of carrying drugs), which remained essentially unchanged during the clinical trial. A secondary objective, the changes in T5SS, did not reach statistical significance. This is likely due to the fact that the sample

size and the power of the study were calculated on a different outcome, i.e. the HRQoL parameter. Of note, this would imply that to see an effect on HRQoL, smaller numbers of patients are needed than when using symptom scores. In addition, our results further support the observation that HRQoL does not strictly reflect symptoms [22, 23], and therefore it must be always included in clinical trials. Another important aspect to be considered is the possible impact of the treatment of PER on concomitant asthma, in the context of the United Airways Disease [24]. In this regard, the results are conflicting: some trials reported a significant effect of the treatment of rhinitis on coexisting asthma [25, 26], whereas a recent meta-analysis including few studies reported no effect [27]. In summary, this is the first study based on a patient's reported outcome, confirming that treating PER can also reduce the impact of concomitant asthma on the QoL, thus supporting the current recommendations for the treatment [1].

Acknowledgements

This study has been partially supported by ARMIA (Associazione Ricerca sulle Malattie Immunologiche e Allergiche). We wish to thank Dr Silvia Geraci for her valuable support in the statistical analyses.

Funding: This trial was sponsored by Schering-Plough Spa, Italy.

Conflict of interest: Giovanni Passalacqua and Giorgio Walter Canonica act as consultants and speakers for Schering Plough. Cristina Le Grazie is an employee of Schering Plough Spa, Italy.

References

- 1 Bousquet J, Van de Cauwenberge P., eds. Allergic rhinitis and its impact on Asthma (ARIA) WHO position paper. *J Allergy Clin Immunol* 2001; 108 (Suppl.): S147–334.
- 2 Demoly P, Allaert FA, Lecasble M, Bousquet JPRAGMA. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). *Allergy* 2003; 58: 672–5.
- 3 Ciprandi G, Cirillo I, Vizzaccaro A *et al*. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy* 2005; 60:882–7.
- 4 Blanc PD, Trupin L, Eisner M *et al*. The work impact of asthma and rhinitis: findings from a population-based survey. *J Clin Epidemiol* 2001; 54:610–8.
- 5 Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. *J Allergy Clin Immunol* 2007; 120:381–7.
- 6 Schoenwetter WF, Dupclay L Jr, Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin* 2004; 20:305–17.
- 7 Baiardini I, Pasquali M, Giardini A, Majani G, Canonica GW. Quality of life in respiratory allergy. *Allergy Asthma Proc* 2001; 22:177–81.
- 8 Bousquet J, Neukirch F, Bousquet PJ *et al*. Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol* 2006; 117:158–62.
- 9 Bousquet J, Annesi-Maesano I, Carat F *et al*. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. *Clin Exp Allergy* 2005; 35:728–32.
- 10 Cruz A. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy* 2007; 62 (Suppl. 84):1–41.
- 11 U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research and U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for Industry: patient reported outcome measures: use in medical product development to support labelling claims: draft guidance.

- Health Qual Life Outcomes* 2006; 4: 79.
- 12 European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP)., Reflection paper on the regulatory guidance for the use of health-related quality of life (HROL) measures in the evaluation of medicinal products. European Medicines Agency website, 2005. Available at <http://www.emea.europa.eu/pdfs/human/ewp/13939104en.pdf> (accessed 12 April 2007).
 - 13 Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. *J Allergy Clin Immunol* 1999; 104:364–9.
 - 14 Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999; 14:32–8.
 - 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 Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ* 1998; 317: 1624–9.
 - 17 Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. *Allergy* 2008; 63:1280–91.
 - 18 Global initiative for the management of asthma (GINA). Revised version 2006. Available at <http://www.ginasthma.org> (accessed 10 May 2007).
 - 19 Baiardini I, Braidò F, Tarantini F *et al.* ARIA-suggested drugs for allergic rhinitis: what impact on quality of life? A GA2LEN review. *Allergy* 2008; 63:660–9.
 - 20 Baiardini I, Bousquet PJ, Brzoza Z *et al.* Recommendations for assessing patient-reported outcomes and health-related quality of life in clinical trials on allergy: a GA(2)LEN taskforce position paper. *Allergy* 2009; 65:290–5.
 - 21 van Drunen C, Meltzer EO, Bachert C, Bousquet J, Fokkens WJ. Nasal allergies and beyond: a clinical review of the pharmacology, efficacy and safety of mometasone furoate. *Allergy* 2005; 60:5–19.
 - 22 Juniper EF, Price DB, Stampone PA, Creemers JP, Mol SJ, Fireman P. Clinically important improvements in asthma-specific quality of life, but no difference in conventional clinical indexes in patients changed from conventional beclomethasone dipropionate to approximately half the dose of extrafine beclomethasone dipropionate. *Chest* 2002; 121:1824–32.
 - 23 Ciprandi G, Canonica WG, Grosclaude M, Ostinelli J, Brazzola GG, Bousquet J. Effects of budesonide and fluticasone propionate in a placebo-controlled study on symptoms and quality of life in seasonal allergic rhinitis. *Allergy* 2002; 57:586–91.
 - 24 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.
 - 25 Pedersen W, Hjulær I, Bisgaard H, Mygind N. Nasal inhalation of budesonide from a spacer in children with perennial rhinitis and asthma. *Allergy* 1998; 53: 383–7.
 - 26 Baena-Cagnani CE, Berger WE, DuBuske LM *et al.* Comparative effects of desloratadine versus montelukast on asthma symptoms and use of beta 2-agonists in patients with seasonal allergic rhinitis and asthma. *Int Arch Allergy Immunol* 2003; 130:307–13.
 - 27 Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. *Cochrane Database Syst Rev* 2003; 003570.