

Original article

Effects of budesonide and fluticasone propionate in a placebo-controlled study on symptoms and quality of life in seasonal allergic rhinitis

Background: Intranasal glucocorticosteroids are effective in seasonal allergic rhinitis. This study compared the efficacy of budesonide (Rhinocort®Turbuhaler®) and fluticasone propionate (Flixonase®) in this respect.

Methods: Patients ($n=280$) were randomized to receive budesonide, 140 µg (delivered dose) once daily, fluticasone, 200 µg once daily, or matching placebos for 5 weeks. The primary efficacy variable was the change in combined nasal symptom (nasal blockage, runny nose, sneezing) scores. Quality of life was measured in 121 patients by means of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and the Short-form Health Survey (SF-36).

Results: Both steroids significantly reduced combined nasal symptoms, compared with placebo. There was no significant difference between the two treatments. Substantial or total symptom control was achieved in 89.9% of the budesonide-treated patients, compared with 88.7% with fluticasone and 42.7% with placebo. Four of the five domains of the RQLQ were significantly improved with budesonide, whereas with fluticasone only two domains were improved. Budesonide significantly improved scores in five out of eight domains of the SF-36, whereas no domains were improved with fluticasone.

Conclusion: There was no significant difference in efficacy between budesonide and fluticasone in this study. However, greater improvements in quality of life were seen with budesonide than with fluticasone.

**G. Ciprandi¹, W. G. Canonica¹,
M. Grosclaude², J. Ostinelli³,
G. G. Brazzola⁴, J. Bousquet⁵**

¹Università degli Studi di Genova, Genova, Italy;

²Guilherand Granges; France; ³AstraZeneca, Rueil-Malmaison, France; ⁴AstraZeneca, Italy; ⁵Hôpital Arnaud de Villeneuve, Montpellier Cedex, France

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Professor J. Bousquet
Hôpital Arnaud de Villeneuve
371 avenue du Doyen Gaston Giraud
34295 Montpellier Cedex 5
France

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Seasonal allergic rhinitis is very common and in addition to the classic rhinitis symptoms of nasal blockage, rhinorrhea, itching, and sneezing, patients have an impaired quality of life (1). The Rhinitis Quality-Of-Life questionnaire (RQLQ) has been used in several trials testing the effect of nasal glucocorticosteroids in seasonal allergic rhinitis (2–6). In these studies, QOL was found to be improved by treatment.

The treatment of seasonal allergic rhinitis is mainly based on antihistamines and topical glucocorticosteroids (1). Budesonide is a glucocorticosteroid that has been used for several years for the topical treatment of asthma and rhinitis, and has been shown to be effective and safe (7). The dry powder formulation (Rhinocort Turbuhaler®) of budesonide, which consists of the active substance only, has been shown to be effective and safe in the treatment of grass pollen-induced allergic rhinitis at metered doses of 200 µg and 400 µg taken once daily (8). The corresponding delivered doses from this device are about 70% of the metered (9), i.e. approximately 140 µg and 280 µg.

Fluticasone propionate, another glucocorticosteroid,

is available for topical nasal use in an aqueous formulation, at a recommended dose of 200 µg, given once daily (10,11).

In a study of patients with perennial allergic rhinitis, intranasal budesonide 140 µg and 280 µg (delivered doses) and fluticasone propionate 200 µg were compared. No significant differences were seen between the active treatments while all three were significantly more effective than placebo (12).

The aim of the present study was to compare the efficacy of 140 µg once daily budesonide dry powder with 200 µg once daily fluticasone propionate aqueous suspension in patients with seasonal allergic rhinitis by means of using combined and individual nasal symptom scores and HRQL assessments.

Material and methods

Study design

There was no blinding between treatments but the active and placebo treatments were blinded with respect to each other by the use of a masking device; the budesonide treatment (Turbuhaler®) differed in

appearance from the fluticasone propionate treatment (aqueous spray). Patients were assigned to parallel treatment groups according to a computer-generated block randomization list.

The study involved 10 centres in France and 9 in Italy. The HRQL assessment was performed in the French centres only. The study comprised a 1-week screening period, a 1-week run-in period, and a 5-week treatment period.

Patients

Patients with an age range from 18 to 69 years, with a history of seasonal rhinitis for at least 2 years and allergic to grass and/or *Parietaria* pollens were studied. Pollen allergy was verified by positive skin-prick test (SPT), RAST or CAP system tests. Only patients with moderate to severe rhinitis were included. They had to have symptoms requiring at least antihistamine treatment during the previous pollen season and to have at least two nasal symptoms (blocked nose, runny nose or sneezing) recorded during the run-in period. Patients were excluded if they had concomitant perennial allergic rhinitis, signs of active infection, or structural abnormalities in the nose. Pregnant or breast-feeding women were likewise excluded. No topical, systemic or depot steroid treatment was permitted within the 6 weeks before the run-in period. Antihistamines had to be stopped within 48 h (astemizole 8 weeks) prior to visit 1. Each patient gave written consent to participate. The study was approved by the Local Ethics Committees and was performed in accordance with the principles stated in the Declaration of Helsinki.

Treatment

During the screening, run-in and treatment periods, patients were only allowed to use antihistamine tablets (cetirizine, 10 mg OD) and eye drops (disodium cromoglycate) as rescue medications. Patients eligible for inclusion were then randomized to one out of four treatments for 5 weeks: budesonide 140 µg delivered dose (Rhinocort Turbuhaler® 100 µg metered dose, AstraZeneca, Lund, Sweden: one inhalation in each nostril every morning); fluticasone propionate 200 µg (Flixonase® 50 µg, GlaxoSmithKline, Uxbridge, UK: 2 sprays in each nostril every morning); placebo budesonide Turbuhaler® or placebo fluticasone propionate (administered in the same fashion as the active treatments). No concomitant medication, apart from the rescue medications, was allowed during the study.

Assessments

All patients recorded daily symptoms on a diary card throughout the study period. Nasal symptoms (blocked nose, runny nose, sneezing), as well as eye symptoms, were assessed every evening and scored as follows: 0=no symptoms; 1 = mild symptoms, not troublesome; 2 = moderate symptoms, frequently troublesome but not enough to interfere with normal daily activity or night-time sleep; 3 = severe symptoms, troublesome enough to interfere with normal daily activity or night-time sleep. Intake of study medication and the use of antihistamine rescue medication were also recorded in the diary.

At clinic visits at the start, and after 2 and 5 weeks of the treatment, information on adverse events was collected by means of a standard question: 'Have you had any health problems or symptoms not usually associated with your seasonal allergic rhinitis since your last visit?', and a nasal examination was performed. At the end of the treatment period, patients were asked to make an overall evaluation of the treatment efficacy according to a 5-grade scale, where 0 = aggravated symptoms and 1, 2, 3 and 4 referred to no, minor, substantial and total control of symptoms, respectively.

Quality of Life assessment

Patients' HRQL was assessed in the French centres, using three questionnaires; the specific rhinitis questionnaire, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (13), the generic health status questionnaire, and the Medical Outcome Study Short-Form Health Survey (SF-36) questionnaire (14), all of which were administered at the end of run-in and again after the treatment period. The questions referred to the week prior to the visit at the clinic, and patients were required to mark their responses on an ordinal scale or to answer 'yes/no'.

The RQLQ has 24 items which are divided into six domains: activities (three items), sleep (three items), general problems (seven items), practical problems (three items), nose problems (four items) and emotional state (four items). The SF-36 questionnaire is based on 36 items selected to represent nine health concepts (physical and social functioning, role limitations in physical and emotional problems, mental health, vitality, bodily pain, general, general perception of health, change of health).

Pollen counts

Pollen counts were recorded for all centres in a standardized way throughout the study period and it was found that grass and/or *Parietaria* pollen were present during the period of the study.

Statistical analysis

The primary efficacy variable was the combined nasal symptom score (the sum of the three individual nasal symptom scores). The mean value of this variable, as well as the mean values of individual symptom scores over the 1-week run-in and the 5-week treatment period, were calculated. Changes from the baseline in the mean combined nasal symptom scores were compared using ANOVA, with treatment, center and baseline score factors as covariates in the model, followed by pairwise comparisons.

ANOVA was also used for the analyses of the secondary efficacy variables: changes in individual nasal symptom scores; patients' overall evaluation of treatment efficacy at the end of the study, and the use of cetirizine as a rescue medication.

The HRQL questionnaires were analyzed using the change from the beginning to the end of treatment. Changes were compared between treatments using an ANOVA model, which included the factors treatment, center, and baseline QoL scores as covariates.

Compliance was assessed as the number of doses marked as taken in the diaries relative to the number of doses according to the protocol and the proportion was analyzed using the Kruskal-Wallis test.

In all tests of significance two-tailed alternatives were used. $P < 0.05$ was considered statistically significant.

Table 1. Baseline characteristics for all patients treated

	BUD (n=104)	FP (n=102)	Placebo (n=101)	All (n=307)
Age mean (years)	34.3	34.3	34.9	34.5
Range	17–59	18–69	18–64	17–69
Weight mean (kg)	66.7	65.9	66.6	66.4
Range	45–113	47–90	43–96	43–113
Height mean (cm)	169	169	169	169
Range	148–190	150–194	148–192	148–194
Rhinitis				
Duration mean (no. of years)	11.6	10.5	11.5	11.2
Range	1–34	1–48	1–50	1–50

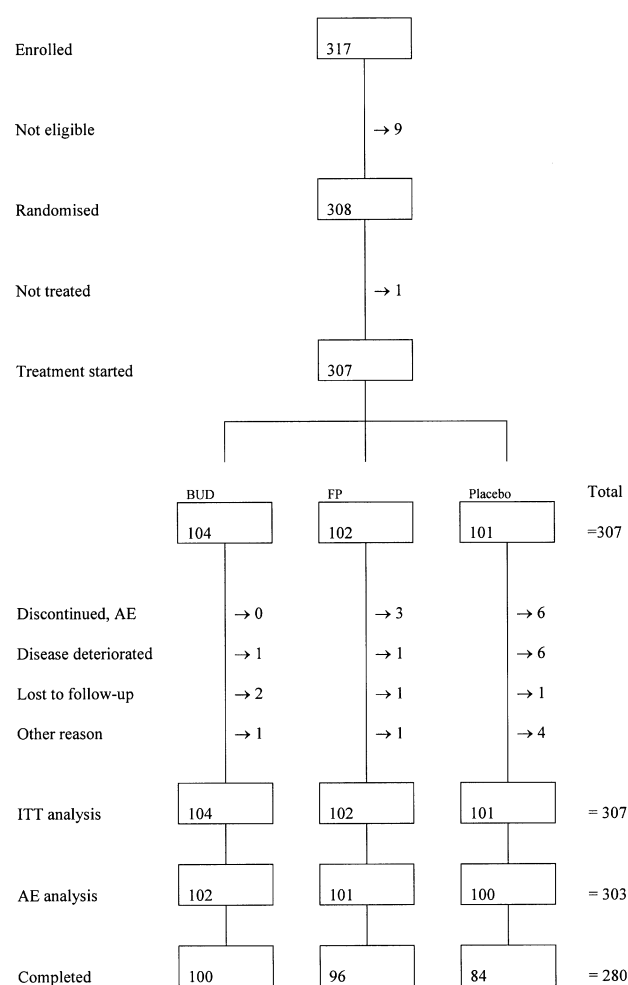


Figure 1. Patient distribution.

Results

Patient population

A total of 308 patients were randomized, 307 (152 males, 155 females) were treated (one patient was lost to follow up), and 280 patients completed the 5-week study. For the HRQL assessments (at the French centres only) data from 121 patients were available. The treatment groups were comparable as regards sex distribution, age and duration of disease (Table 1).

Clinical efficacy

A total of 307 patients were evaluated and included in the Intention To Treat (ITT) analysis (Fig. 1). The mean baseline period was 7.2 days (range 3–23) and the mean treatment period was 35 days (range 1–58).

Combined nasal symptoms In the two placebo groups, the combined nasal symptom scores were only minimally changed from baseline values and were very similar (Fig. 2). Hence, the two placebo groups were combined for statistical analyses. In the two actively

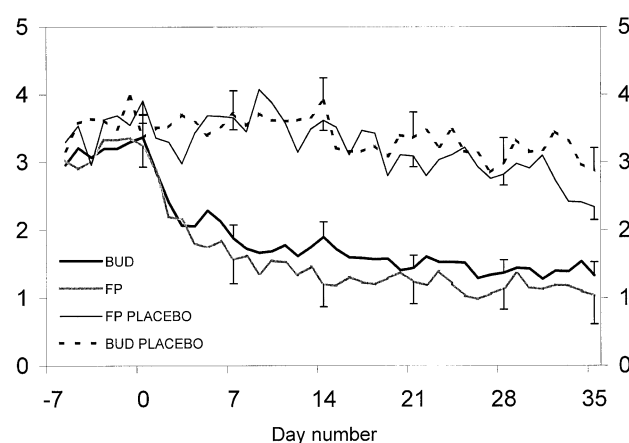


Figure 2. Daily means incl S.E.M of Combined Nasal Symptoms by treatment during run-in (days –6–0) and treatment period (days 1–35).

treated groups, the total symptom score were reduced within the first week and then remained low for the next 4 weeks. Adjusted mean change from baseline was -1.44 and -1.71 for budesonide and fluticasone propionate vs. placebo, respectively. No significant difference in the combined nasal symptom score could be detected between budesonide and fluticasone propionate ($P=0.11$).

Individual nasal symptoms Scores for each separate nasal symptom significantly decreased in the two active treatment groups as compared with the placebo (Table 2). No statistically significant difference between the two active treatment groups was found for individual nasal symptom scores except for nasal blockage ($P=0.039$).

Eye symptoms Scores for eye symptoms significantly decreased in the budesonide treatment group compared with placebo, but not in the fluticasone propionate treatment group. No significant difference between the two active treatment groups was found for eye symptom scores (Table 3).

Rescue medication The baseline consumption of antihistamine rescue medication was low (mean 2.58, 2.78 and 2.86 tablets per week in the budesonide, fluticasone propionate and placebo-treated groups, respectively). Consumption decreased significantly in the two active treatment groups by comparison with placebo. However, the budesonide-treated patients consumed significantly fewer antihistamine tablets (mean 1.23 tablets/week) compared with the fluticasone propionate group (mean 1.93 tablets/week) during the treatment period ($P=0.030$).

Patients' overall evaluation of treatment efficacy The overall assessment of treatment efficacy made by the

Table 2. Change from baseline of individual nasal symptoms

	N	Baseline mean change	Adjusted mean change	95% conf. limits	P-value
Blocked nose					
Change from baseline					
BUD	102	1.05	-0.47	-0.56-0.37	
FP	101	1.08	-0.61	-0.71-0.51	
Placebo					
Treatment comparison	100	1.22	-0.02	-0.12 0.08	
BUD vs. FP		0.14	0.01	0.27	0.039
BUD vs. placebo		-0.45	-0.59	-0.31	<0.001
FP vs. placebo		-0.59	-0.73	-0.46	<0.001
Runny nose					
Change from baseline					
BUD	102	1.12	-0.50	-0.59-0.40	
FP	101	1.04	-0.58	-0.68-0.49	
Placebo					
Treatment comparison	100	1.20	0.02	-0.08 0.11	
BUD vs. FP		0.09	-0.04	0.22	0.19
BUD vs. placebo		-0.51	-0.65	-0.38	<0.001
FP vs. placebo		-0.60	-0.73	-0.47	<0.001
Sneezing					
Change from baseline					
BUD	102	1.04	-0.53	-0.62-0.45	
FP	101	1.05	-0.59	-0.67-0.50	
Placebo					
Treatment comparison		1.12	-0.04	-0.12 0.04	
BUD vs. FP	100	0.05	-0.07	0.17	0.39
BUD vs. placebo		-0.49	-0.61	-0.38	<0.001
FP vs. placebo		-0.54	-0.66	-0.43	<0.001

patients at the last visit showed significantly better results in the two active treatment groups than in the placebo group ($P<0.001$), with no significant difference between budesonide and fluticasone (Fig. 3).

Compliance with study medication Compliance was 92.6% in the budesonide group, 96.0% in the fluticasone group, and 96.6% in the placebo group, with no significant difference between the two active treatment groups ($P=0.097$).

Health-related quality of life Mean baseline scores for the RQLQ and the SF-36 are summarized, together with changes between baseline and end of treatment.

RQLQ Four out of the five domains, i.e., sleep problems, nonhayfever problems, practical problems and nasal symptoms, were significantly improved following budesonide treatment compared with placebo (sleep; $P=0.009$, nonhayfever, practical, and nasal symptoms; $P<0.001$). The fifth dimension, emotional problems, also showed some improvement, but the result was not significant. Only two out of the five domains (practical problems and nasal symptoms) were improved following fluticasone propionate treatment compared with placebo ($P=0.003$). The two active treatment groups did not differ significantly from each other.

Table 3. Change from baseline of eye symptoms

	N	Baseline mean change	Adjusted mean change	95% conf. limits	P-value
Change from baseline					
BUD	102	0.69	-0.22	-0.31-0.14	
FP	101	0.66	-0.17	-0.26-0.08	
Placebo	100	0.77	-0.06	-0.15 0.03	
Treatment comparison					
BUD vs. FP		-0.05	-0.17	0.07	0.41
BUD vs. placebo		-0.16	-0.28	-0.04	0.009
FP vs. placebo		-0.11	-0.23	0.01	0.075

SF-36 questionnaire Five out of the eight domains relating to general quality of life, i.e., physical functioning, vitality, social functioning, role-emotional and mental health, were significantly improved following budesonide treatment, compared with placebo, but there were no significant changes following fluticasone propionate treatment. The two active treatment groups did not differ significantly from each other (Table 4).

The aggregated summary scores Physical Component Summary (PCS) and Mental Component Summary (MCS) are presented in Table 4. The two active treatment groups did not show any significant difference compared with placebo for PCS. For the MCS only the budesonide group showed significant improvements ($P<0.05$) compared with placebo. No significant difference between the two active treatment groups were seen.

Safety

Adverse events From the 307 patients who received study medication, four did not return for any clinic visit, thus 303 patients were eligible for the safety

Overall Assessment at last visit

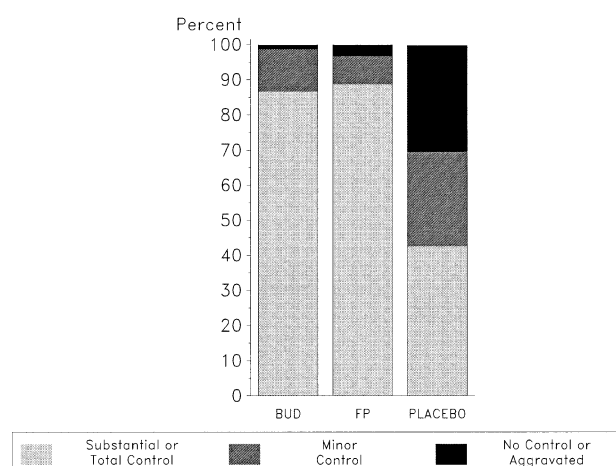


Figure 3. Overall assessment of treatment efficacy at the end of the study.

Table 4. Quality of Life dimensions at baseline and changes from baseline to end of treatment

RQLQ Questionnaire	BUD		FP		Placebo	
	Baseline <i>n</i> =39	Change	Baseline <i>n</i> =40	Change	Baseline <i>n</i> =37	Change
Sleep problems	1.62	−0.99*	1.48	−0.74	1.53	−0.26
Non hay fever symptoms	1.52	−0.90**	1.26	−0.53	1.27	−0.11
Practical problems	3.24	−1.94**	2.95	−1.68*	2.96	−0.73
Nasal problems	3.01	−1.78**	2.65	−1.33*	2.70	−0.53
Emotional problems	2.12	−0.62	1.69	−0.36	1.82	−0.28
SF-36 Questionnaire	<i>n</i> =41		<i>n</i> =42		<i>n</i> =38	
Physical functioning	88.7	4.6*	95.5	0.5	92.9	−0.7
Role physical	80.5	5.9	84.1	7.4	88.2	0.8
Bodily pain	79.0	3.6	83.0	4.6	82.8	−1.1
General health	70.1	1.1	79.0	1.1	78.8	−2.7
Vitality	58.0	6.8*	60.4	5.1	64.1	0.9
Social functioning	67.3	8.3*	72.1	5.1	72.4	0.2
Role emotional	79.2	8.4*	85.4	4.3	87.4	−3.9
Mental health	65.0	7.8*	70.0	4.5	72.7	0.3
Physical Component Summary (PCS)	52.2	0.7	54.5	0.7	54.2	−0.6
Mental Component Summary (MCS)	44.2	4.6**	46.5	2.5	48.0	−0.4

**P* < 0.05; ** *P* < 0.001.

analysis. Adverse events were mild and reported by 15% of the patients who were treated with budesonide, 12% treated with fluticasone propionate, and 15% treated with placebo. Only one patient in the budesonide group and two in the fluticasone group complained of episodes of blood-tinged nasal discharge.

Discussion

In the present study we found that the two nasal glucocorticosteroids were equally effective against nasal symptoms of seasonal allergic rhinitis. General quality of life was improved by budesonide but not by the fluticasone propionate. For disease-specific quality of life budesonide improved twice as many domains as fluticasone propionate. For the primary efficacy variable, the combined nasal symptom score, no significant difference between the two active treatment groups was found. A 0.14 score step difference for nasal blockage was found to be significantly different when comparing fluticasone propionate with budesonide. Not only the doses, but also the presentations (aqueous spray vs. dry powder inhaler) differed between the treatments. There were no significant differences concerning nasal symptom scores between the respective placebo groups, indicating that differences in formulation were unlikely to have influenced the result. The results of the present study in seasonal allergic rhinitis are in line with a similar comparison in perennial allergic rhinitis (12), in which intranasal budesonide dry powder 140 µg and fluticasone propionate aqueous suspension at a higher dose of

200 µg had similar clinical efficacy. The primary efficacy variable, the combined nasal symptom score, decreased during a 5-week treatment, with no significant difference between the two active treatment groups. This study shows that the two nasal corticosteroids are effective in persistent allergic rhinitis induced by pollen. The magnitude of symptom-score reduction (approximately 1.5 score steps) was considered clinically relevant, and all three components of the combined nasal score contributed equally to the reduction.

The clinical relevance of the small difference in scores for blocked nose between the two active treatment groups is, however, uncertain.

As seen in Fig. 2, the efficacy of the active treatments tend to discriminate mean scores from placebo from the first day. During the second week of treatment the active treatments reach a mean separation to placebo, which is not superseded later in the 5-week period.

With regard to health-related quality of life, this study further showed that both generic and disease-specific HRQL are impaired in patients with seasonal allergic rhinitis and can be improved by suitable therapy. The Quality of Life assessment indicated budesonide 140 µg (delivered dose) to be clearly superior to placebo; four out of the five disease-specific domains of the RQLQ and five out of the eight general domains of the SF-36 questionnaire were significantly improved with budesonide. In contrast, fluticasone propionate 200 µg significantly improved only two out of the five disease-specific domains and was not statistically significantly superior in any domain in the generic SF36 questionnaire. In view of the burden allergic rhinitis creates not

only for the patient, but also for the national economy in terms of medical care and lost productivity (15), it is important to consider these wider implications of drug efficacy on patient well-being.

All statistical findings were well above the 0.5 score step difference vs. placebo that has been suggested to be the minimal clinical relevant change for RQLQ (16).

In conclusion, the efficacy of topical budesonide dry powder 140 µg taken once daily, was not significantly different to fluticasone propionate aqueous suspension 200 µg taken once daily, for the primary efficacy variable in seasonal allergic rhinitis. Improvement in general and disease-specific HRQL was significantly superior to placebo in the budesonide group. Both active treatments were well tolerated.

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