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Efficacy and tolerability of budesonide aqueous nasal spray in chronic rhinosinusitis patients*

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SUMMARY

This study evaluated the efficacy and tolerability of budesonide in an aqueous nasal spray (BANS) in patients with chronic rhinosinusitis. In this double-blind, placebo-controlled, multicentre, parallel-group study, patients (n=167) with persistent rhinosinusitis symptoms despite 2-weeks' antibiotic treatment were randomised to receive BANS 128 μg b.i.d. or placebo for 20 weeks. Morning combined symptom scores (CSS) in patients receiving BANS decreased by a mean of –1.85 (95% CI –2.27, –1.43), versus –1.02 (–1.43, –0.61) in the placebo group (p=0.005); corresponding values for evening CSS were –1.78 (–2.22, –1.35) and –1.02 (–1.45, –0.60), respectively (p=0.012). BANS produced significant reductions in nasal congestion and discharge scores, and improved patients' sense of smell (morning only), versus placebo. Peak nasal inspiratory flow (PNIF) increased significantly during BANS treatment. In allergic patients, BANS significantly (p<0.001) reduced both morning –1.40 (–2.18, –0.62) and evening –1.37 (–2.15, –0.58) CSS from baseline versus placebo, but changes in non-allergic patients (morning: –0.04 [–0.95, 0.87]; evening: 0.14 [–0.81, 1.09]) were not significant. PNIF was significantly (p<0.01) increased in both allergic and non-allergic patients from baseline versus placebo. BANS is an effective and well-tolerated treatment for chronic rhinosinusitis.

Key words: chronic sinusitis, topical corticosteroid, randomized trial

INTRODUCTION

The term 'rhinosinusitis' denotes an inflammatory reaction in the lining of the nasal and paranasal sinuses, which also involves the nasal cavity to a greater or lesser extent. Rhinosinusitis is characterised by major symptoms, such as nasal congestion or obstruction, mucopurulent nasal discharge, and facial pain or headache, as well as minor symptoms such as cough or halitosis. Although definitions of rhinosinusitis may not be globally acknowledged, the condition has generally been defined as acute, sub-acute, chronic, and acute-on-chronic, according to the duration of symptoms; thus, chronic rhinosinusitis is defined as symptoms persisting for at least 3 months (Lanza and Kennedy, 1997).

Chronic rhinosinusitis has traditionally been treated with combinations of antibiotics, anti-inflammatory agents and anti-allergy therapies, together with decongestants and saline douches. However, partly due to difficulties in defining the condition and establishing a clinically relevant patient population, few controlled trials of medical therapy have been undertaken.

Budesonide aqueous nasal spray (BANS: Rhinocort® Aqua™, AstraZeneca Lund, Sweden) is a topical nasal formulation of the anti-inflammatory corticosteroid budesonide, which has been shown to be effective in patients with seasonal and perennial allergic rhinitis (Creticos et al., 1998; Meltzer, 1998; Stern et al., 1998; Day et al., 2000) and nasal polyposis (Tos et al., 1998; Jankowski et al., 2001). Given the efficacy of BANS in other inflammatory nasal conditions, it might be anticipated that this preparation would also be effective in patients with chronic rhinosinusitis. Hence, the present controlled study was performed to evaluate the efficacy and tolerability of BANS in patients with chronic rhinosinusitis.

METHODS

The trial was a randomised, double-blind, placebo-controlled study performed at 19 centres: the United Kingdom (n=7; Ear,

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Nose and Throat [ENT] specialists); Hungary (n=6: ENT specialists); South Africa (n=6: ENT specialists [n=5], medical centre [n=1]). Patients at 18 of the centres were seen by ENT specialists and patients at one of the South African centres were evaluated in a medical centre. Patients participated in the study at different times over a 3-year period, minimising the possible influence of seasonal allergic rhinitis. The study was approved by local Ethics Committees at all centres and was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before inclusion in the study.

Protocol

Patients were eligible for inclusion in the study if they were aged 18 years or over, and had chronic rhinosinusitis, which was defined as at least two major symptoms for at least 12 weeks. Major symptoms were facial pain, pressure or headache; facial congestion, nasal blockage or nasal obstruction; purulence or discolored discharge; and impaired sense of smell. None of the patients included had nasal polyposis. Patients with structural nasal abnormalities, severe complicated bacterial rhinosinusitis, dental problems, or other medical conditions that could affect the diagnosis of rhinosinusitis were excluded, as were patients who had undergone sinonasal surgery within the previous 12 months. Other exclusion criteria included unstable asthma requiring high doses of inhaled corticosteroids; current immunotherapy for allergic rhinitis; topical or systemic steroid therapy within 4 or 8 weeks, respectively, of screening; antihistamine use within 48 hours, or astemizole use within 8 weeks, prior to screening; regular use of decongestants within 1 month prior to screening; antibiotic treatment within 1 week prior to screening.

All patients underwent a 3-week run-in period. During the first 2 weeks of this period, patients received antibiotic treatment with co-amoxiclav, 250/125 mg t.d.s. or, in the cases of penicillin-sensitivity, 6% of patients were given erythromycin, 500 mg b.i.d.; no treatment was given during the third week. At the end of the run-in period, patients with chronic rhinosinusitis symptoms during the last 7 days of the run-in period, showing at least one symptom with a symptom score of 2 or more on a 4-point scale (see below) on 4 of the last 7 days, were randomised to receive BANS 128 μg (64 μg in each nostril b.i.d.), or placebo for 20 weeks. Courses of antibiotic treatment, with the same regimens used during the run-in period, could be given for 2 weeks if needed to treat exacerbations (defined as episodes of worsening symptoms that required a course of antibiotic therapy).

Patients kept diary records of chronic rhinosinusitis symptoms (facial pain, pressure or headache; facial congestion, nasal obstruction or blockage; nasal discharge; impairment of sense of smell) throughout the run-in and treatment periods. With the exception of sense of smell, symptoms were scored on a 4-point scale (0=no symptoms; 1=mild symptoms present, but not troublesome; 2=moderate symptoms that were frequently troublesome but not sufficiently so to interfere with normal daily activities or sleep; 3=severe symptoms that interfered with normal daily activities or sleep). Sense of smell was scored as follows: 0=no impairment; 1=slight impairment; 2=moderate impairment; 3=absent. Patients were also required to record use of antibiotics and compliance with study medication in their diary cards. In addition, patients provided an overall evaluation of efficacy at 4-week intervals, beginning 4 weeks after the start of randomised treatment. This evaluation was recorded on a 5-point scale (0=no control over symptoms; 1=minor control; 2=moderate control; 3=substantial control; 4=total control).

Peak nasal inspiratory flow (PNIF) was measured in all patients at all centres, by peak flow meter (Clement Clarke International, Harlow, UK). Measurements were taken at clinic visits, at the beginning and end of the run-in period, and every 4 weeks during randomised treatment. The best of three readings was recorded on each occasion. Information about exacerbations of rhinosinusitis was also recorded at these clinic visits.

Computed tomography (CT) scanning was performed on all patients during the third week of the run-in period. The anterior ethmoid, posterior ethmoid, frontal, sphenoid and maxillary sinuses on each side were scored on a 3-point scale (Lund and Mackay, 1993) (0=no abnormality; 1=partial opacification; 2=total opacification). The ostiomeatal complex was scored as 0 (not occluded) or 2 (occluded). The maximum possible score was 24.

English-speaking patients completed the Chronic Sinusitis Survey (Gliklich and Metson, 1995; Metson and Gliklich, 2000) on entry to the study and at the end of the randomised treatment period; a validated version of the questionnaire in Hungarian was not available. In addition, all patients completed the SF-36 health-related quality of life questionnaire (Ware and Sherbourne, 1992) at the same times.

Information about adverse events (AEs) was obtained by standard open questioning at all clinic visits. In addition, a physical examination and nasal examination were performed at the beginning of the run-in period and at the end of the study. The initial physical examination included skin prick tests against extracts of house dust mite (Dermatophagoides pteronyssinus and D. farinae), cat, dog, Alternaria, Cladosporum, grass-, weed- and tree-pollen. A positive response to allergen was defined as a mean wheal diameter at least half that of a histamine control, and at least 3 mm greater than a negative control. Blood was obtained for routine haematology and clinical chemistry tests at the beginning and end of the run-in period and at the end of the study.

The primary efficacy measure was the combined symptom score, which was calculated as the sum of the scores for four groups of symptoms: facial pain, pressure or headache; facial congestion, nasal obstruction or blockage; nasal discharge; impairment of the sense of smell. Changes in mean combined symptom score from the last week of the run-in period to the

20-week treatment period were analysed by analysis of variance with treatment and country as factors and baseline mean score as covariate. Secondary analyses were performed on individual symptom scores, patients' overall evaluation of efficacy and PNIF data. These analyses were based on the change in mean scores from the end of the run-in period to the end of randomised treatment. The time to the first exacerbation in each group was compared between treatments using the log rank test. Since no previous study has used a combined symptom score for chronic rhinosinusitis, the sample size was determined from experience in previous studies using this approach in patients with allergic rhinitis, in which the standard deviation of the sum of 4 nasal symptoms was approximately 1.75. On this basis, it was calculated that a sample size of approximately 50 evaluable patients per group would provide 80% power to detect a difference of 1.0 in the combined symptom score between treatments, assuming an α-level of 0.05 and a two-sided test.

Assignment

Patients were allocated a treatment number in consecutive order and randomisation was performed in balanced blocks of four by means of a computer program (SAS Software version 6.11) at the Department of Biostatistics and Data Management, AstraZeneca R&D Lund, Sweden. All randomised patients were included in the intention-to-treat analysis.

Blinding

BANS and placebo aqueous sprays were identical in appearance and were both administered via the same vehicle. The treatment codes were known only to the persons responsible for packaging, who were not involved in the study in any other way. Each bottle of study medication was supplied with a detachable label, which was attached to the Case Report Form when the medication was dispensed.

RESULTS

A total of 244 patients were enrolled in the study. Of these, 77 discontinued during the run-in period (some patients discontinued for more than one reason); 66 did not meet the eligibility criteria in terms of symptom severity, seven withdrew because of AEs and one because of disease deterioration; three were lost to follow-up and four discontinued for other reasons. Thus, 167 patients were eligible for randomisation, of whom 81 were randomised to BANS and 86 to placebo. In total, 134 patients (67 in each group) completed treatment.

Table 1. Patient demographic characteristics.

	BANS (n=81)	Placebo (n=86)
Mean age, years (range)	38 (19–65)	43 (18–78)
Males/females	35/46	41/45
Caucasian/black/other	75/2/4	79/4/3
Mean height, cm (range)	171.3 (153–200)	170.2 (153–190)
Mean weight, kg (range)	76.7 (48–120)	73.2 (50–106)

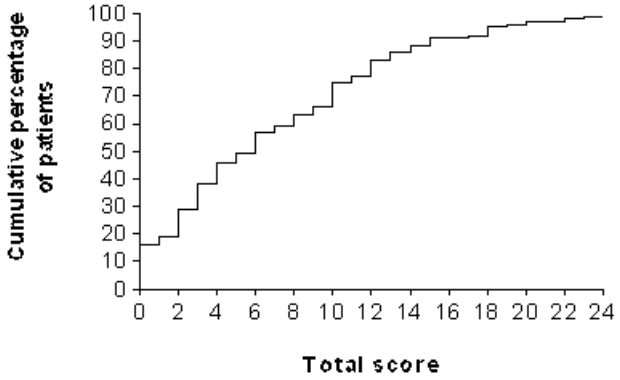

Figure 1. Cumulative computed tomography score at baseline.

The baseline demographic characteristics of the randomised patients were similar in the two groups (Table 1). Overall, 97 patients showed negative skin prick tests to all allergens tested and 69 showed positive responses to at least one allergen. The total CT score ranged from 0–24 (Figure 1). The majority of patients had partial opacification and 26 patients had a normal CT scan at baseline (score=0).

Efficacy

Changes in mean combined symptom scores are shown in Figure 2. The adjusted mean change in combined morning symptom scores from baseline to week 20 was −1.85 (95% CI −2.27, −1.43) in patients receiving BANS, compared with −1.02

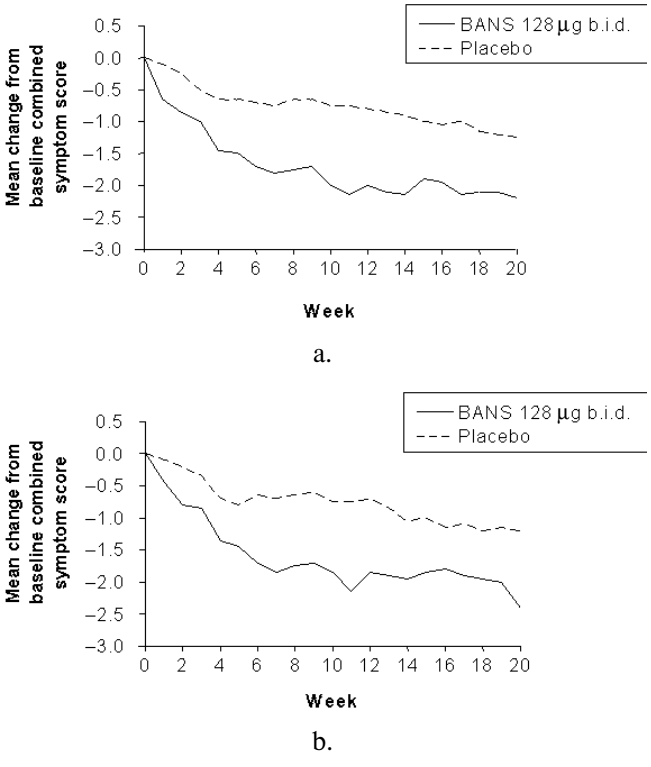

Figure 2. Changes in a) morning and b) evening combined symptom scores.

Table 2a. Changes in individual rhinosinusitis symptom score from baseline.

	BANS		Placebo		Difference (BANS – placebo)	p-value
	Baseline mean	Adjusted mean change (95% CI)	Baseline mean	Adjusted mean change (95% CI)		
Facial pain/pressure/headache						
(morning)	1.38	–0.38 (–0.5, –0.26)	1.33	–0.25 (–0.37, –0.13)	-0.13 (-0.29, 0.04)	0.139
(evening)	1.40	–0.39 (–0.51, –0.26)	1.33	–0.29 (–0.42, –0.17)	-0.09 (-0.26, 0.08)	0.287
Facial congestion/nasal blockage/ obstruction						
(morning)	1.88	–0.67 (–0.80, –0.54)	1.85	–0.34 (–0.47, –0.21)	-0.33 (-0.51, -0.15)	<0.001
(evening)	1.75	–0.60 (–0.74, –0.46)	1.78	–0.33 (–0.46, –0.20)	-0.27 (-0.46, -0.09)	0.004
Nasal discharge						
(morning)	1.48	–0.50 (–0.63, –0.38)	1.47	–0.29 (–0.41, –0.17)	-0.21 (-0.38, -0.04)	0.016
(evening)	1.43	–0.51 (–0.64, –0.39)	1.41	–0.25 (–0.37, –0.13)	-0.26 (-0.43, -0.09)	0.003
Impairment in sense of smell						
(morning)	1.43	–0.32 (–0.46, –0.19)	1.27	–0.14 (–0.27, –0.01)	-0.18 (-0.37, 0.0)	0.047
(evening)	1.38	–0.30 (–0.43, –0.16)	1.25	–0.12 (–0.26, 0.01)	-0.17 (-0.35, 0.01)	0.066

(–1.43, –0.61) in the placebo group (p=0.005) (Figure 2a); corresponding values for evening symptom scores were –1.78 (–2.22, –1.35) and –1.02 (–1.45, –0.60), respectively (p=0.012) (Figure 2b). Changes in individual symptom scores are summarised in Table 2a. BANS treatment was associated with a significant decrease in scores for all monitored symptoms except facial pain and sense of smell (in the evening), compared with placebo. No differences in response between patients were noted at individual centres or by country.

The mean number of exacerbations was 1.3 in the BANS group and 1.1 in the placebo group, and the mean time to the first exacerbation was 56 days in both groups. No statistical analysis was performed due to the low frequency of exacerbations. There was also no significant difference between the groups in the proportion of antibiotic-free days in each group (median 99.3% in each group; p=0.61).

At the end of the study, 43.1% of patients treated with BANS reported substantial or total control of their symptoms, compared with 25.9% of placebo-treated patients. Over the entire study period, the patients' assessment of treatment control over symptoms was significantly better in the BANS group than in the placebo group (p=0.015).

The mean improvement in total Chronic Sinusitis Survey scores was 7.35 (95% CI 1.64, 13.06) in the BANS group and 4.51 (–1.10, 10.12) in the placebo group; there was no significant difference between the treatments (mean difference 2.84, 95% CI –5.08, 10.75; p=0.4781). There was a significant improvement in the general health subscale of the SF-36 questionnaire in BANS-treated patients, compared with placebo, but no other significant differences were observed.

During the course of the study, PNIF increased by a mean of 49.1 L/min in the BANS group, compared with 10.4 L/min in the placebo group. The difference between the groups was statistically significant (p<0.001).

Although the study was powered only for the primary analysis, two exploratory, pre-planned, subgroup analyses were performed. One subgroup analysis examined changes in symptom scores in patients with CT evidence of opacification (CT score ≥1) at baseline. In these patients (n=141), BANS produced mean reductions in morning and evening combined symptom scores of –0.66 (95% CI –1.32, –0.01; p=0.048) and –0.53 (–1.20, 0.14; p=0.117) respectively, from baseline, compared with placebo, which are comparable with those seen in the overall patient population. The other subgroup analysis compared the response to treatment in allergic and non-allergic patients. In allergic patients (n=76), BANS treatment reduced morning and evening combined symptom scores compared with baseline by

Table 2b. Change in peak nasal inspiratory flow from baseline for allergic and non-allergic patients.

		Change from baseline Adjusted mean change	p-value
Allergic patients	BANS (n=44)	65.3	–
	Placebo (n=47)	21.0	–
	BANS vs placebo	44.3	0.003
Non-allergic patients	BANS (n=34)	44.2	–
	Placebo (n=35)	9.3	–
	BANS vs placebo	34.9	0.002

a mean of –1.40 (95% CI –2.18, –0.62; p=0.001) and –1.37 (–2.15, –0.58; p=0.001), respectively, compared with placebo. In non-allergic patients (n=67) the changes in morning and evening combined symptom scores compared with baseline in BANS-treated patients were –0.04 (–0.95, 0.87) and 0.14 (–0.81, 1.09), respectively, compared with placebo, and did not reach statistical significance. BANS produced significant improvement in PNIF, compared with placebo, both in allergic (p=0.003) and non-allergic (p= 0.002) patients (Table 2b).

Tolerability

A total of 169 AEs (BANS n=88, placebo n=81) were reported by 85 patients (BANS n=39, placebo n=46). There were only minor differences in AE profiles between the two groups (Table 3) and there was no statistically significant difference in the number of patients experiencing a respiratory infection. Most AEs were mild or moderate in severity; five (BANS n=1, placebo n=4) were regarded as serious, none of which were considered to be due to study medication. Importantly, there was no increase in the incidence of infection or mucopurulent secretions in patients treated with BANS. There were no significant differences in vital signs, haematology or clinical chemistry between the two groups.

Table 3. Number of patients reporting adverse events (%).

	BANS (n=81)	Placebo (n=86)
Respiratory infection	11 (13.6)	7 (8.1)
Headache	5 (6.2)	7 (8.1)
Blood-tinged secretions	8 (9.9)	3 (3.5)
Viral infections	5 (6.2)	4 (4.7)
Pharyngitis	3 (3.37)	4 (4.7)
Sinusitis	1 (1.2)	5 (5.8)
Flu-like disorder	4 (4.9)	2 (2.3)
Pain	4 (4.9)	2 (2.3)
Rhinitis	4 (4.9)	2 (2.3)
External ear infection	2 (2.5)	3 (3.5)

DISCUSSION

The results of this randomised controlled trial show that intranasal treatment with BANS 128 µg b.i.d. is efficacious in patients with chronic rhinosinusitis. In previous studies, nasal glucocorticosteroids have been used as an adjunct to antibiotic therapy, with demonstrable efficacy on symptoms of sinusitis (Meltzer et al., 1993; Meltzer et al., 2000). Nasal steroids are also effective in chronic polyposis; conventional aqueous nasal spray treatment is effective in a once-daily regimen (Jankowski et al., 2001), although multiple or higher doses and special procedures are sometimes required (Richards et al., 1999). The present study, however, is the first randomised trial to have prospectively evaluated the use of intranasal budesonide as first-line therapy in a population of patients with the diagnosis of chronic rhinosinusitis.

The patient population was selected on the basis of chronic major symptoms, according to the American Academy of Otorhinolaryngology criteria (Lanza and Kennedy, 1997). The impact of the emphasis on chronic symptoms is reflected in the finding that a relatively large number of enrolled patients were not eligible for randomisation since they did not show the required persistence of symptoms after a course of antibiotic treatment. The patient population in this study can therefore be considered typical of patients initially presenting in primary care with persistent, troublesome, symptoms. In addition, the relevance of the population is underlined by the finding that the majority of patients had signs of rhinosinusitis visible as CT abnormalities at baseline. The prevalence of sensitisation to allergens noted in the study population (approximately 40%) is consistent with the known prevalence of allergies in patients with chronic rhinosinusitis (approximately 40–50%) (Spector, 1992).

The principal efficacy measure used in this study was the change in the combined symptom score. This reflects the fact that chronic rhinosinusitis is defined clinically by the presence of a cluster of symptoms, rather than by any single symptom. Based on the accepted definition of chronic rhinosinusitis (Lanza and Kennedy, 1997), the four major symptoms were chosen to form the combined score, in order to include relevant and measurable clinical responses. The finding that BANS produced significant improvement in this combined score therefore shows that such treatment can produce clinically meaningful symptom relief.

The analysis showed that BANS treatment produced significant improvement in PNIF in these patients with chronic rhinosinusitis. In placebo-treated patients with rhinitis, the decrease in PNIF during allergen provocation, compared with BANS-treated patients, is approximately 30–14 L/min (Day et al., 2000). In view of this, the finding that BANS treatment increased PNIF by 49 L/min indicates a clinically relevant improvement in nasal patency.

Disappointingly, it was not possible to demonstrate a significant effect of treatment on the Chronic Sinusitis Survey, a disease-specific quality of life measure. This may be at least partly attributable to the restrictions on medication use in this study; since the Chronic Sinusitis Survey comprises separate domains for sinusitis symptoms and medication use, its ability to reflect the overall impact of treatment may have been reduced under these circumstances. Patients scored their quality of life, measured using the SF-36 questionnaire, similarly to patients with asthma, a condition with a documented impact on quality of life (Bousquet et al., 1994); however, even if treatment had a positive effect, only one domain, general health, showed a significant improvement compared with the placebo group. This may reflect limitations of the technique rather than a lack of difference between treatments; it is well established that the SF-36 provides a sensitive measure of the impact of illness on quality of life, but is less suitable for longitudinal assessments of the impact of treatment. In a previous study in patients with chronic rhinosinusitis, SF-36 scores at baseline were comparable to those in the present study, but significant improvements

in disease-specific symptoms and in all subscales of patient-perceived global health were observed after endoscopic sinus surgery (Winstead and Barnett, 1998).

Efficacy was analysed separately in two subgroups. In the population with CT changes consistent with chronic rhinosinusitis, in addition to clinical symptoms and signs, significant efficacy was demonstrated against morning symptoms, despite the fact that the study was under-powered for this analysis. Separate analyses in the allergic and non-allergic groups showed, interestingly, that despite the fact that only the allergic subgroup demonstrated an improvement in symptom scores, there was a statistically significant improvement in the objective PNIF measurement in both groups. This suggests that there is an effect of treatment in non-allergic patients that is not readily detectable from symptom scores. Thus, some clinical benefit may be obtained even in non-allergic patients.

Treatment with BANS was well tolerated. To set the incidence of blood-tinged discharge in perspective, the treatment time should be considered: the incidence was similar to that seen in considerably shorter studies in patients with allergic rhinitis. It is noteworthy that the incidence of infection or mucopurulent secretions was not increased in the BANS group, since this has previously been a general concern with the use of steroids to treat infections.

In conclusion, the results of this study show that BANS, 128 μg b.i.d., is effective in reducing symptoms and improving PNIF for patients with chronic rhinosinusitis.

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