REVIEW ARTICLE

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Comparative Clinical Studies with Ebastine

Efficacy and Tolerability

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Abstract

Ebastine is a nonsedating and selective histamine H_1 receptor antagonist without anticholinergic or sedative effects at therapeutic doses. It has shown a rapid onset and long duration of action, and doses of 10 and 20mg once daily are effective in relieving the nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis (SAR and PAR, respectively).

In 3 randomised double-blind, multicentre clinical trials in patients with SAR, ebastine 10 and 20mg once daily for 2 to 3 weeks significantly reduced symptoms (nasal discharge, stuffiness, sneezing, itchy nose, itchy/watery eyes) when compared with placebo. Similarly, in patients with PAR, two 3-week studies demonstrated that ebastine 10mg twice daily and 20mg once daily significantly relieved the symptoms of PAR, as measured by the Perennial Index.

Ebastine was well tolerated in these studies and had no effect on the QTc interval.

Ebastine is a nonsedating and selective histamine H_1 receptor antagonist with no anticholinergic or sedative effects at therapeutic doses.[1-4] It has shown a rapid onset and long duration of action, and its effectiveness and tolerability at doses of 10 and 20mg once daily in relieving the nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis (SAR and PAR, respectively) have also been demonstrated.[5,6] To date, ebastine has been approved in 28 countries and is currently marketed in 14 countries.

Five controlled clinical trials – 3 in SAR and 2 in PAR – were presented at the International Cardiac Round-Table held in Barcelona in April 1997. A common attribute of these studies was their use of ECGs at baseline and post-treatment, with additional Holter monitoring in some patients. This article summarises clinical experience with ebastine and focuses on efficacy and tolerability, including ECG measurements, in patients with SAR or PAR. In this paper, the efficacy of the studies is assessed by analysis of the primary variables only.

1. Materials and Methods

Studies 01, 02, 03, 04 and 05 were multicentre, placebo-controlled, randomised, double-blind clinical trials designed to assess the efficacy and tolerability of ebastine in patients with SAR or PAR. 12-lead ECGs, with additional Holter monitoring in some patients, were also carried out. Clinical trials 01, 02 and 03 were conducted in patients with SAR, whereas 04 and 05 enrolled patients with PAR. The main characteristics of the studies are shown in table I.

The primary efficacy variable in all the studies was the mean change from baseline in the total

symptom score. In the SAR studies, this score was based on 5 symptoms (nasal discharge, nasal stuffiness, sneezing, itchy nose and itchy/watery eyes), which were measured on a 4-point severity scale and recorded daily by patients. In the PAR studies, the symptom score represents the sum of the scores for nasal discharge, sneezing and itchy nose, also measured daily on a 4-point scale (the Perennial Index).

Tolerability variables were standard laboratory tests, the recording of adverse events and a 12-lead ECG carried out at baseline, at the end of the first week of treatment, at the end of the second week and, in those studies lasting for 3 weeks, at the end of the third week of treatment (all at 3 to 4 hours postdose). Holter monitoring was performed in some patients.

A total of 1563 patients were enrolled in these studies: 498 patients (31.9%) received ebastine 20mg once daily, 335 (21.4%) 10mg once daily, 80 (5.1%) 1mg once daily, 77 (4.9%) 3mg once daily, 74 (4.7%) 10mg twice daily, and 73 (4.7%) 30mg once daily; 426 patients (27.3%) received placebo. A total of 1202 patients (842 receiving ebastine and 360 receiving placebo) had ECG evaluations at both baseline and during the double-blind phase. Holter monitoring was performed in 226 patients.

In studies of SAR, patients were required to have an aggregated symptom score of at least 42 points out of a possible 105 (for all rhinitis symptoms: discharge, nasal stuffiness, sneezing, itchy nose and itchy/watery eyes) for the 3.5 days preceding enrolment, as well as a positive skin test to ragweed allergen. Study 01 evaluated ebastine doses of 1, 3, 10, 20 and 30mg compared with placebo for the relief of symptoms of rhinitis in patients with seasonal ragweed allergy. Study 02 compared ebastine 20mg once daily administered in the morning or evening and 10mg once daily administered in the morning or evening with placebo. The objective of study 03 was to compare ebastine 10mg once daily and 20mg once daily with placebo in patients 12 years and older.

The studies in patients with PAR compared ebastine 10mg twice daily and 20mg once daily with placebo (study 04) and ebastine 20mg once daily with placebo (study 05) in patients 12 years and older. Patients were required to have a minimum total rhinitis symptom score (discharge, sneezing, itchy nose) of 32 out of a possible 63 points over the 3-day screening period plus the morning of the baseline day, as well as a positive skin test to a perennial allergen and a positive nasal smear for eosinophils.

In all studies, patients were also required to have a normal 12-lead ECG without a prolonged QT/QTc (Bazett) interval prior to study entry.

Analysis of the primary efficacy variable was performed according to a 2-way analysis of variance model, with treatment group and centre as main effects. Two-sided t-tests with a level of significance of 0.05 were used to compare treatment means.

2. Results

A total of 1144 patients were included in the SAR studies: 252 received placebo, 80 received ebastine 1mg once daily, 77 ebastine 3mg once daily, 335 ebastine 10mg once daily, 327 ebastine 20mg once daily and 73 ebastine 30mg once daily.

Table I. Key characteristics of clinical trials evaluating the efficacy and tolerability of ebastine in seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR)

Study	Indication	Country	Dose (mg) and timing	Treatment duration (weeks)	Age (years)	No. of patients
01	SAR	USA/Canada	1,3,10,20,30 od	2	18-65	459
02	SAR	USA	20/10am; 20/10pm	3	12-64	396
03	SAR	USA	10, 20 od	3	12-68	289
04	PAR	USA	10 bid, 20 od	3	12-77	224
05	PAR	USA	20 od	3	12-64	195

am = morning; **bid** = twice daily; **od** = once daily; **pm** = afternoon.

Table II. Study 02: Mean reduction from baseline in total symptom score in patients treated with ebastine or placebo for 3 weeks for seasonal allergic rhinitis

Treatment group	No. of patients	Adjusted mean change from baseline (SE)	p-Values *vs* placebo
Ebastine 10mg am	79	–3.49 (0.3)	0.048
Ebastine 20mg am	77	–3.98 (0.3)	0.002
Ebastine 10mg pm	80	–3.11 (0.3)	0.274
Ebastine 20mg pm	77	–3.49 (0.3)	0.049
Placebo	78	–2.65 (0.3)	

am = morning; **pm** = afternoon.

419 patients were enrolled in the PAR trials: 174 were in the placebo group, while 171 patients received ebastine 20mg once daily and 74 received ebastine 10mg twice daily.

A total of 14 patients were excluded from the primary efficacy analysis (study 01: 5; 02: 5; 03: 2; 04: 1; 05: 1) because they failed to record efficacy data in their diaries and, in one patient, because only data relating to clinic visits were available.

2.1 Seasonal Allergic Rhinitis

In study 01, a total of 454 of 459 patients were included in the primary efficacy analysis. The mean (standard error) reductions from baseline in total symptom score over the 2-week period were as follows: –1.9 (0.3), –2.2 (0.3), –2.2 (0.3), –2.6 (0.3), –2.4 (0.3) and –1.7 (0.3) for ebastine 1, 3, 10, 20, 30mg and placebo, respectively. Statistically significant differences versus placebo were found for ebastine 20mg ($p = 0.009$) and 30mg ($p = 0.012$). Moreover, during the first 12-hour period, statistically significant differences were observed for ebastine 3mg [–2.5 (0.3); $p = 0.016$], 10mg [–2.6 (0.3); $p = 0.004$], 20mg [–2.8 (0.3); $p < 0.001$] and 30mg [–2.5 (0.3); $p = 0.001$] in comparison with placebo [–1.5 (0.3)]. With respect to the second 12-hour period, no statistically significant differences were detected [1mg: –1.9 (0.3); 3mg: 1.9 (0.3); 10mg: –1.8 (0.3); 20mg: –2.4 (0.3); 30mg: –2.2 (0.3); placebo: –1.8 (0.3)].

In study 02, 391 of 396 patients were considered for the primary efficacy analysis. The mean reduction from baseline in total 24-hour symptom score over the 3-week treatment period is shown in table II and figure 1. Overall, both ebastine 10mg once daily in the morning and 20mg once daily in the morning or evening demonstrated statistically significant differences in comparison with placebo.

In study 03, 287 patients were considered for the efficacy analysis. Analysis of the change from baseline in symptom scores over 24 hours and the total symptom score showed that a statistically significant difference *vs* placebo was reached for all symptoms (fig. 2). The mean (standard error) reductions in the total symptom score were as follows: –3.76 (0.28), –3.54 (0.28) and –2.05 (0.28) for ebastine 10mg, 20mg and placebo, respectively.

2.2 Perennial Allergic Rhinitis

In study 04, 223 patients were included in the efficacy analysis. The mean (standard error) reductions from baseline in the total symptom score over the 3-week period were as follows: –2.39 (0.21), –2.23 (0.20) and –1.65 (0.21) for ebastine 10mg

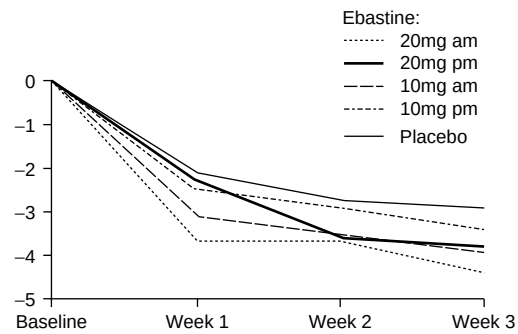

Fig. 1. Study 02: Mean reduction from baseline in symptom scores and in the total symptom score over 24 hours in patients treated for 3 weeks with ebastine 10 or 20mg in the morning (am) or evening (pm), or placebo, for seasonal allergic rhinitis.

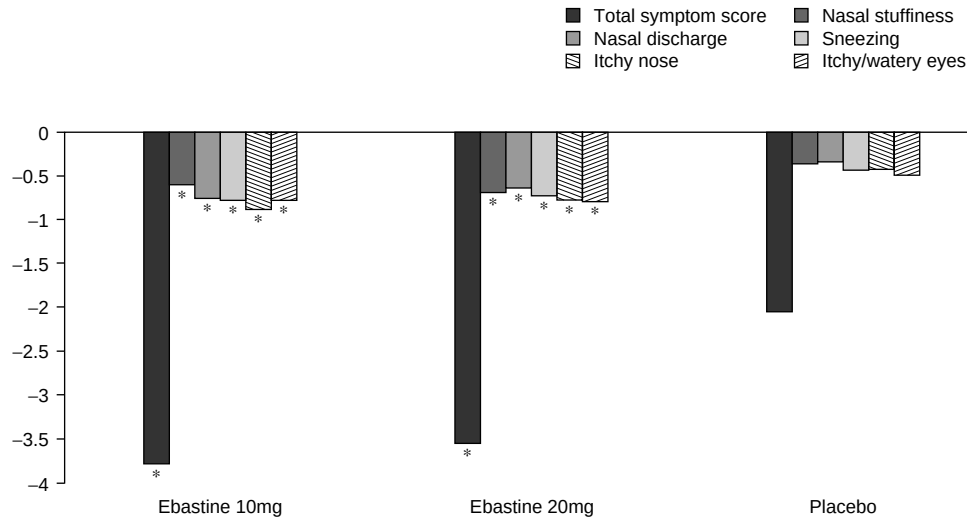

Fig. 2. Study 03: Mean reduction from baseline in symptom scores and in the total symptom score over 24 hours after 3 weeks' treatment with ebastine 10 or 20mg or placebo once daily for seasonal allergic rhinitis. * $p < 0.05$ *vs* placebo.

twice daily, 20mg once daily, and placebo, respectively. Statistically significant differences for ebastine 10mg twice daily ($p = 0.009$) and 20mg once daily ($p = 0.032$) versus placebo were found. Moreover, during the first 12-hour period, statistically significant differences were observed for ebastine 10mg twice daily [–2.35 (0.23); $p = 0.032$], but not for 20mg once daily [–2.17 (0.22); $p = 0.097$] in comparison with placebo [–1.76 (0.23)]. With respect to the second 12-hour period, statistically significant differences were detected [ebastine 10mg twice daily: –2.32 (0.2), $p = 0.008$; 20mg once daily: –2.17 (0.2), $p = 0.028$; placebo: –1.63 (0.2)]. The daily mean reductions in the Perennial Index were greater in the ebastine 10mg twice daily and 20mg once daily groups than in the placebo group for all days in the study, although these differences did not reach statistical significance.

Finally, analysis of the primary efficacy variable in study 05, for which 194 patients were considered, showed that ebastine 20mg significantly reduced the symptoms of PAR versus placebo at all time-points. The adjusted mean changes from baseline (standard error) in the Perennial Index were –2.06 (0.18) and –1.51 (0.17) for ebastine 20mg and placebo ($p = 0.024$), respectively.

A plot of the mean adjusted change from baseline in the primary efficacy variable from the two PAR clinical trials (04 and 05) is shown in figure 3.

2.3 Tolerability

With regard to tolerability, there were no serious adverse events related to the study drug. A total

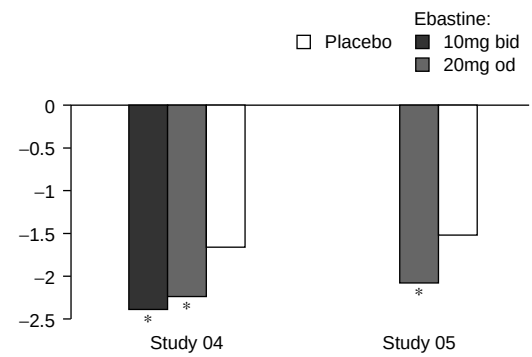

Fig. 3. Mean adjusted change from baseline in the Perennial Index (studies 04 and 05) after 3 weeks' treatment with ebastine 10mg twice daily or 20mg once daily or placebo in patients with perennial allergic rhinitis. **bid** = twice daily; **od** = once daily; * $p < 0.05$ versus placebo.

of 2 patients, one in study 05 (receiving placebo; left knee injury) and another in study 03 (receiving ebastine 10mg; facial paralysis), reported one serious adverse event each. However, in both instances, the investigators determined that these events were unrelated to the study drug. Headache, nausea, tiredness and dry mouth were the most frequently reported adverse events, and their incidence was similar in ebastine and placebo recipients. There were no clinically relevant changes from baseline in laboratory values in either the ebastine or the placebo groups.

No clinically relevant adverse ECG changes were detected. A total of 1202 patients (842 ebastine and 360 placebo recipients) had both baseline and end-of-treatment double-blind ECG evaluations. In particular, no statistically significant differences were found when the mean observed QTc interval of each ebastine group was compared with that of the placebo group. The only exception was for the ebastine 10mg once-daily group: the mean maximum QTc interval for placebo was significantly greater than that for the ebastine 10mg once-daily group (411 *vs* 406 msec); however, this was considered a clinically non-relevant finding. Significant differences were observed in the mean percentage change from baseline for ebastine 10mg once daily, 10mg twice daily, 20mg once daily and placebo (11.01, 10.18, 13.07 and 11.2%, respectively, $p = 0.01$), although these changes were not considered to be clinically relevant. No dose-related changes from baseline in QTc intervals were found.

24-Hour Holter monitoring was performed at baseline and at the end of the study in a total of 226 patients. There were no clinically relevant findings in any of the Holter monitoring data and no serious adverse events occurred in any of these patients.

3. Conclusions

In the clinical trials carried out with ebastine in patients with SAR, analysis of the primary efficacy variable showed that ebastine 10 and 20mg once daily significantly reduced the symptoms of SAR when compared with placebo.

Similarly, in the two 3-week studies, 04 and 05, analysis of the primary efficacy variable, the Perennial Index, demonstrated that ebastine 10mg twice daily and 20mg once daily significantly relieved the symptoms of PAR in comparison with placebo.

With regard to issues of tolerability, analyses of the 5 clinical trials showed that ebastine had no effect on the QTc interval at the recommended doses, and that it was well tolerated in patients with SAR and PAR.

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