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Meta-Analysis of the Efficacy of Ebastine 20 mg Compared to Loratadine 10 mg and Placebo in the Symptomatic Treatment of Seasonal Allergic Rhinitis

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Key Words
Ebastine · Loratadine · Meta-analysis · Seasonal allergic rhinitis · Symptoms

Abstract
Background: Few randomized studies have compared the efficacy of ebastine and loratadine in the symptomatic treatment of seasonal allergic rhinitis (SAR). ***Methods:*** A meta-analysis was performed on data from four randomized, double-blind, placebo-controlled, parallel-group clinical trials comparing the efficacy of ebastine 20 mg once daily versus loratadine 10 mg once daily in the symptomatic treatment of SAR symptoms. Primary efficacy variable was the mean change in the overall mean daily reflective total symptom score (TSS), i.e. the sum of five rhinitis symptom scores: nasal discharge, nasal congestion, nasal itching, sneezing and total eye symptoms (itchy/watery eyes) over the first 2 weeks of treatment compared to baseline. ***Results:*** There were 2,089 patients in the population analyzed: 749, 739 and 601 patients in the ebastine 20 mg, loratadine 10 mg and placebo groups, respectively. Compared to baseline, overall mean daily reflective TSS over the first 2 weeks of treatment was –3.61 (35.4% reduction from baseline) in the ebastine group, –3.05 (29.0% reduction) in the loratadine group and –2.30 (22.7% reduction) in the placebo group. Statistically significant differences in the mean change from baseline were found when comparing ebastine and loratadine ($p < 0.001$), ebastine and placebo ($p < 0.0001$), and loratadine and placebo ($p < 0.0001$). The global effect (i.e. the difference in overall mean daily reflective TSS over the first 2 weeks of treatment) of ebastine compared with loratadine over the first 2 weeks of treatment was –0.56 (95% confidence interval, CI, –0.86 to –0.26), and it was sustained during the whole (4-week) period studied. The global effects of ebastine and loratadine compared with placebo were –1.30 (95% CI, –1.61 to –0.99) and –0.74 (95% CI, –1.05 to –0.43), respectively. Secondary variables (reflective and snapshot individual symptom scores) showed the same trend. ***Conclusions:*** This meta-analysis confirms that ebastine 20 mg has a good efficacy profile, inducing a greater decrease from baseline in mean rhinitis symptom scores than loratadine 10 mg or placebo.

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Introduction

Ebastine is a long-acting second-generation H_1-receptor antagonist available for the first-line treatment of allergic rhinitis in more than 40 countries worldwide [1, 2]. The efficacy of ebastine has been reported in several placebo-controlled and comparative trials on the symptomatic treatment of perennial [3, 4] and seasonal allergic rhinitis (SAR) [5–9]. Loratadine is another H_1-receptor antagonist available worldwide for SAR [10]. Some studies have compared the pharmacodynamic effects of ebastine and loratadine [11–13]. Overall, these studies have shown greater pharmacodynamic effects of ebastine 20 mg compared to loratadine 10 mg in the histamine-induced skin reaction test. However, few randomized studies have compared the efficacy of ebastine and loratadine in the symptomatic treatment of SAR patients [3, 8, 9]. The objective of this meta-analysis based on data reported in four clinical trials (CM 30 [14], CM 31 [9], GMA 402 [15] and M/EBS/28 [16]) performed during the clinical development of ebastine was to confirm whether ebastine 20 mg once daily is clinically and statistically different from loratadine 10 mg once daily in the symptomatic treatment of SAR, as well as to obtain a precise estimate of treatment effect, measured by the reduction in both the total symptom score and individual symptoms in a large patient population.

Patients and Methods

Study Designs

Initially, eight studies were assessed as they fulfilled the main inclusion criteria, i.e. comparative clinical trial studying the treatment of SAR, and randomized, double-blind and parallel-group design. Nevertheless, four studies were excluded: one study due to lack of precision in describing the primary efficacy variable, another one because the dose of ebastine was flexible from 20 to 10 mg and vice versa, and two studies due to the use of other criteria as the primary variable. Therefore, this meta-analysis was based on the results obtained from four studies carried out under the same protocol: all were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies comparing the efficacy and safety of ebastine 20 mg once daily versus loratadine 10 mg once daily in the treatment of SAR symptoms [9, 14–16]. All the studies were carried out in the United States during ragweed pollen season. The treatment period was 4 weeks; however, as FDA guidelines recommend that SAR treatments be assessed using data from the first 2 weeks of treatment, only data from the first 2 weeks were used for the main assessment of efficacy in this meta-analysis.

Study Population and Efficacy Variables

The study population consisted of all randomized patients included in the four studies who presented at baseline daily score data (reflective scores) for all rhinitis symptoms [nasal discharge, nasal congestion, nasal itching, sneezing and total eye symptoms (itchy/watery eyes)], and at least symptom daily score data for some day after starting the treatment.

Prior to dosing in the morning and before bedtime, the patient rated the five rhinitis symptoms (nasal discharge, nasal congestion, nasal itching, sneezing and total eye symptoms) and scored them numerically on a scale from 0 to 3, where 0 = symptom absent, 1 = mild, 2 = moderate and 3 = severe. In every case, the patient rated the symptoms over the previous 12-hour period (reflective score) and at the time of recording (snapshot score).

The primary efficacy variable was the mean change in overall mean daily reflective total symptom score (TSS, sum of all five rhinitis symptom scores) over the first 2 weeks of treatment compared to baseline. The baseline averages were calculated from 3 of the 4 days preceding randomization with the highest bedtime and next morning reflective TSS. Secondary efficacy variables were change from baseline in overall mean daily reflective TSS over the 1st week of treatment, over 3 weeks and over the entire treatment period (4 weeks), as well as the changes in reflective and snapshot individual symptom scores.

Statistical Analysis

For each study, the primary and secondary efficacy variables were analyzed by means of an ANOVA model [17–19]:

$$Y_{istd} - Y_{ist\ baseline} = \mu + T_t + e_{istd}$$

where Y_{istd} was the overall mean value of variable Y for patient *i* from study *s* receiving treatment *t* over a time period *d* (d = 1–4 weeks), $Y_{ist\ baseline}$ was the baseline value of variable Y for patient *i* from study *s* receiving treatment *t*, μ was the grand mean, T_t was the treatment fixed effect (t = 1–3), e_{istd} was the residual term for patient *i* from study *s* receiving treatment *t* for the period *d* (d = 1–4 weeks), where $e_{istd} \sim N(0,\sigma^2_e)$.

When the treatment factor in the ANOVA model was statistically significant ($p < 0.05$), two-sided treatment comparisons were done: the primary comparison was ebastine 20 mg versus loratadine 10 mg, whereas secondary comparisons were done between both active treatments and placebo. Treatment effects and treatment differences were estimated using the least square (LS) means together with their standard errors (SE) and 95% confidence intervals (CI). The main results of the four studies assessed are shown in table 1.

In order to estimate the global treatment effect across trials for the primary and secondary efficacy variables, the following ANOVA model [17–19] was used:

$$Y_{istd} - Y_{ist\ baseline} = \mu + T_t + S_s + S * T_{st} + e_{istd}$$

where Y_{istd} was the overall mean value of variable Y for patient *i* from study *s* receiving treatment *t* over a time period *d* (d = 1–4 weeks), $Y_{ist\ baseline}$ was the baseline value of variable Y for patient *i* from study *s* receiving treatment *t*, μ was the grand mean, T_t was the treatment fixed effect (t = 1–3), S_s was the study fixed effect (where s = 1–4), $S*T_{st}$ was the study-by-treatment interaction fixed effect, e_{istd} was the residual term for patient *i* from study *s* receiving treatment *t* for the period *d* (d = 1–4 weeks), where $e_{istd} \sim N(0,\sigma^2_e)$.

Before estimating the global treatment effect, the homogeneity of data across trials was tested by means of the study-by-treatment interaction of the above-described ANOVA model [19, 20]. When

Table 1. Main characteristics of the studies included in the meta-analysis

Study	Patients			LS mean change from baseline (SE) in TSS over the whole treatment period (4 weeks)		
	ebastine 20 mg	loratadine 10 mg	placebo	ebastine 20 mg	loratadine 10 mg	placebo
CM 30 [14]	141	139	140	–3.80 (0.24)	–3.41 (0.24)	–2.55 (0.24)
CM 31 [9]	143	140	139	–4.26 (0.24)	–3.57 (0.25)	–2.57 (0.25)
GMA 402 [15]	183	182	181	–3.71 (0.21)	–3.36 (0.21)	–2.61 (0.22)
M/EBS/28 [16]	282	278	141	–3.73 (0.17)	–2.97 (0.17)	–2.94 (0.24)

LS mean for the change from baseline in the ANOVA model with the factor treatment as a fixed effect.

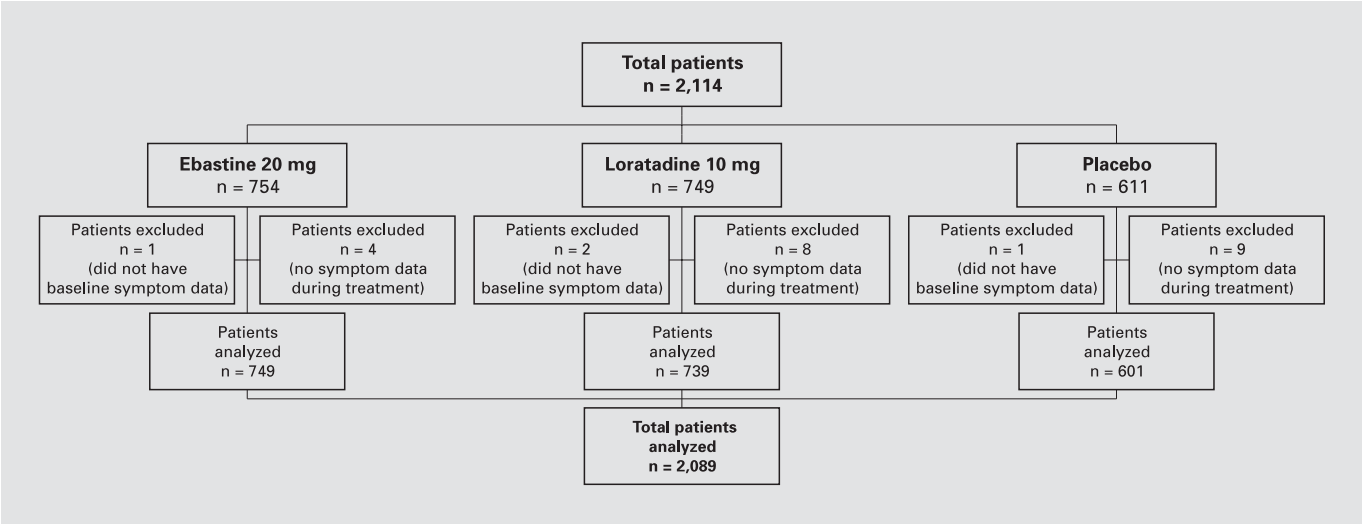

Fig. 1. Distribution of the patients.

the interaction was not statistically significant ($p < 0.10$), the studies were judged homogeneous, and then they were pooled [21, 22]. If the p value of the study-by-treatment interaction was statistically significant ($p < 0.10$), the possible heterogeneity across studies was explored in detail [23].

When the treatment factor in the second ANOVA model was statistically significant ($p < 0.05$), two-sided treatment comparisons were done. Once again, the primary comparison was ebastine 20 mg versus loratadine 10 mg, whereas secondary comparisons were done between both active treatments and placebo. Treatment effects and treatment differences were estimated by LS means, SE and 95% CI.

Sensitivity analyses of the primary efficacy variable were done in order to check the robustness of the meta-analysis: one analysis included the use of an ANOVA model excluding one study at a time [21], and another analysis used an ANOVA mixed model assuming that study and study-by-treatment interaction effects of the ANOVA model were random [20, 23, 24]. If the results of these two approaches yielded similar estimates to those obtained from the ANOVA fixed model, the results of the meta-analysis were considered to be consistent and robust.

Results

Study Population

A total of 2,114 patients were enrolled in the four trials used for this meta-analysis. However, 4 patients were excluded from the analysis because they did not have baseline symptom data, and another 21 patients because they had no symptom data during the entire treatment period. Therefore, the total number of patients analyzed was 2,089: 749 patients were treated with ebastine 20 mg, 739 with loratadine 10 mg and 601 with placebo. Figure 1

Table 2. Baseline characteristics of the patients

Characteristics	Ebastine 20 mg (n = 749)	Loratadine 10 mg (n = 739)	Placebo (n = 601)
Age, years	37.4 ± 13.2	37.6 ± 13.7	36.8 ± 13.6
Gender			
Male	334 (44.6%)	334 (45.2%)	297 (49.4%)
Female	415 (55.4%)	405 (54.8%)	304 (50.6%)
Race			
Black	56 (7.5%)	54 (7.3%)	49 (8.2%)
Caucasian	583 (77.8%)	569 (77.0%)	459 (76.4%)
Hispanic	102 (13.6%)	103 (13.9%)	79 (13.1%)
Oriental	2 (0.3%)	5 (0.7%)	10 (1.6%)
Other	6 (0.8%)	8 (1.1%)	4 (0.7%)
Weight, pounds	170.2 ± 40.1	171.1 ± 42.0	171.5 ± 41.6
Height, inches	66.6 ± 3.9	66.6 ± 4.1	66.7 ± 4.1
Reflective daily TSS	10.08 ± 2.55	10.14 ± 2.54	9.92 ± 2.53
Snapshot daily TSS	9.60 ± 2.89	9.70 ± 2.82	9.39 ± 2.83

Data shown are means ± SD. No significant differences were found between groups.

Table 3. Changes in LS mean daily reflective TSS over the first 2 weeks of treatment compared to baseline

	Mean change from baseline			Global effect			
	n	LS mean (SE)	mean change from baseline, %	vs. placebo		vs. loratadine 10 mg	
				LS mean (SE)	95% CI	LS mean (SE)	95% CI
Ebastine 20 mg	749	–3.61 (0.11)	–35.4	–1.30 (0.16)	–1.61 to –0.99 p < 0.0001	–0.56 (0.15)	–0.86 to –0.26 p < 0.001
Loratadine 10 mg	739	–3.05 (0.11)	–29.0	–0.74 (0.16)	–1.05 to –0.43 p < 0.0001		
Placebo	601	–2.30 (0.12)	–22.7				

LS mean for the change from baseline in the ANOVA model with the factors treatment, study and treatment-by-study interaction as fixed effects.

shows the distribution of these patients and table 2 summarizes the main baseline characteristics. No significant differences in baseline data were found between groups.

Changes in the Primary Efficacy Variable

Mean change from baseline in the primary efficacy variable, overall mean daily reflective TSS, over the first 2 weeks of treatment was –3.61 (35.4% reduction from baseline) in the ebastine 20 mg group, –3.05 (29.0% reduction) in the loratadine 10 mg group, and –2.30 (22.7% reduction) in the placebo group. Statistically significant differences were found in the mean change from baseline between ebastine and loratadine ($p < 0.001$), ebastine and placebo ($p < 0.001$), and loratadine and placebo ($p < 0.0001$; table 3).

The global effect, defined as the difference in overall mean daily reflective TSS, of ebastine 20 mg compared with loratadine 10 mg in the treatment of SAR over the first 2 weeks of treatment was –0.56 (95% CI, –0.86 to –0.26; table 3). This global effect of ebastine 20 mg compared to loratadine 10 mg on TSS was sustained during the entire 4-week study period (fig. 2). Furthermore, the global effect of ebastine 20 mg compared with placebo was –1.30 (95% CI, –1.61 to –0.99), and the global effect of loratadine compared with placebo was –0.74 (95% CI, –1.05 to –0.43).

The treatment-by-study interaction was not statistically significant ($p = 0.167$). Therefore, the four studies were considered homogeneous, and pooling was appropriate. The results of the two sensitivity analyses – the

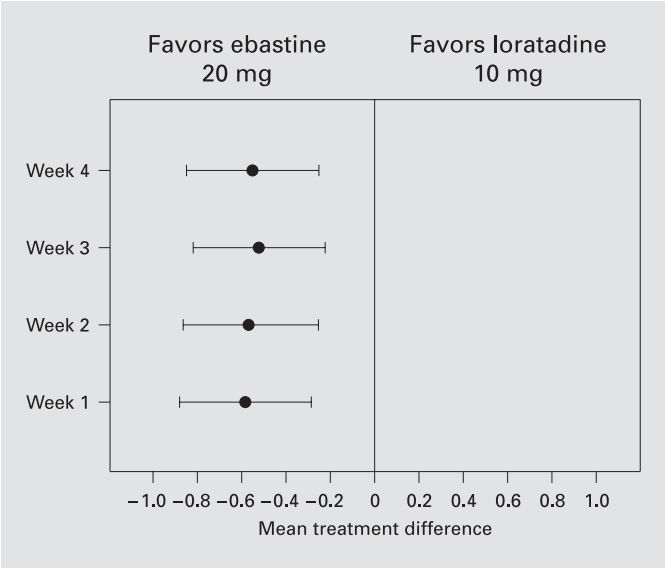

Fig. 2. Mean (95% CI) difference between ebastine 20 mg and loratadine 10 mg in the mean change from baseline for the TSS over the whole treatment period studied (from week 1 to week 4).

ANOVA model excluding one study at a time and the ANOVA fixed model – were similar to those obtained from the main analysis. Therefore, the results of the meta-analysis were considered statistically robust.

Changes in Secondary Efficacy Variables

Over the first 2 weeks of treatment, ebastine 20 mg showed a significantly higher reflective score reduction than loratadine 10 mg for each of the five rhinitis symptoms assessed: nasal discharge (–0.14, $p < 0.0001$), nasal congestion (–0.10, $p = 0.0047$), sneezing (–0.12, $p = 0.0012$), nasal itching (–0.09, $p = 0.0117$) and total eye symptoms (–0.11, $p = 0.0046$; table 4). The symptoms in which ebastine 20 mg had the lowest and highest effects compared with loratadine 10 mg were nasal itching and nasal discharge, respectively. Moreover, both active treatments showed significant differences compared to placebo in each of the five symptom scores assessed (table 4).

The analysis of snapshot symptom scores over the first 2 weeks of treatment showed similar results as those found with the reflective ones. The ebastine global effect versus loratadine for the individual symptoms ranged from –0.14 to –0.09 for both reflective and snapshot scores. Mean reductions from baseline ranged from 25.6 to 42.3% (reflective scores) and from 25.2 to 41.5% (snapshot scores) in the ebastine group compared to 22.3–31.9% (reflective scores) and 20.3–29.4% (snapshot scores) in the loratadine group.

The analysis of reflective symptom scores over 1, 3 or 4 weeks of treatment showed results similar to those found over 2 weeks of treatment.

Discussion

Few studies comparing the effects ebastine and loratadine at doses of 20 and 10 mg, respectively, on SAR symptoms of have been published. One study with a treatment period of 2 weeks including 306 patients showed that ebastine 20 mg once daily, but not loratadine 10 mg once daily, was significantly more effective than placebo both in the overall efficacy evaluation and in the individual evaluation of symptomatology; only the symptom 'blocked nose' did not show significant improvement [8].

A second study evaluated the efficacy and safety of ebastine 20 mg versus loratadine 10 mg administered for a longer term (4 weeks) in 565 patients. Ebastine 20 mg produced significantly greater ($p < 0.05$) reductions in the mean daily reflective (42.5 vs. 36.3%) and mean morning snapshot (40.3 vs. 31.3%) TSS from baseline compared with loratadine 10 mg over the entire treatment period. The overall improvement in daily reflective and morning snapshot TSS was comparable between ebastine 10 mg and loratadine 10 mg and significantly better than placebo ($p < 0.05$) [9]. This second trial had a 4-week double-blind treatment period, a study design long enough to treat rhinitis symptoms throughout the ragweed season as well as to assess treatment tolerance. Unfortunately, the results found in that study could not be compared to those of previous trials due to the difference in treatment duration. For sustained efficacy, a difference was found between ebastine 20 mg and loratadine 10 mg after 4 weeks of treatment, but this finding has to be confirmed by future clinical trials.

The present meta-analysis provides more precise 95% CI intervals for the assessment of the global effect of ebastine 20 mg once daily over loratadine 10 mg once daily. Moreover, the patient population analyzed (2,089 in total) is the largest population of SAR patients studied to date. The global effect of ebastine 20 mg compared with loratadine 10 mg on the reflective total symptom score for the first 2 weeks of treatment was –0.56 (95% CI –0.86 to –0.26), i.e. a 35.4% reduction from baseline for patients treated with ebastine and a 29.0% reduction from baseline for patients treated with loratadine. The snapshot

Table 4. Changes in all LS mean individual daily reflective symptom scores over the first 2 weeks of treatment compared to baseline

	Mean change from baseline			Global effect			
	n	LS mean (SE)	mean change from baseline, %	vs. placebo		vs. loratadine 10 mg	
				LS mean (SE)	95% CI	LS mean (SE)	95% CI
Nasal discharge							
Ebastine 20 mg	743	–0.70 (0.03)	–30.4	–0.24 (0.04)	–0.31 to –0.16 p < 0.0001	–0.14 (0.04)	–0.21 to –0.07 p < 0.0001
Loratadine 10 mg	737	–0.56 (0.03)	–23.3	–0.10 (0.04)	–0.17 to –0.02 p = 0.0095		
Placebo	597	–0.46 (0.03)	–18.8				
Nasal congestion							
Ebastine 20 mg	748	–0.64 (0.02)	–25.6	–0.20 (0.04)	–0.27 to –0.13 p < 0.0001	–0.10 (0.03)	–0.17 to –0.03 p = 0.0047
Loratadine 10 mg	738	–0.54 (0.02)	–22.3	–0.10 (0.04)	–0.17 to –0.03 p < 0.0001		
Placebo	599	–0.44 (0.03)	–19.0				
Sneezing							
Ebastine 20 mg	727	–0.77 (0.03)	–42.3	–0.31 (0.04)	–0.39 to –0.23 p < 0.0001	–0.12 (0.04)	–0.19 to –0.05 p = 0.0012
Loratadine 10 mg	730	–0.65 (0.03)	–31.9	–0.19 (0.04)	–0.27 to –0.11 p < 0.0001		
Placebo	596	–0.46 (0.03)	–18.8				
Nasal itching							
Ebastine 20 mg	728	–0.74 (0.03)	–37.8	–0.25 (0.04)	–0.33 to –0.18 p < 0.0001	–0.09 (0.04)	–0.16 to –0.02 p = 0.0117
Loratadine 10 mg	723	–0.64 (0.03)	–29.0	–0.16 (0.04)	–0.24 to –0.09 p < 0.0001		
Placebo	590	–0.48 (0.03)	–22.5				
Total eye symptoms							
Ebastine 20 mg	738	–0.76 (0.03)	–37.7	–0.31 (0.04)	–0.38 to –0.23 p < 0.0001	–0.11 (0.04)	–0.18 to –0.03 p = 0.0046
Loratadine 10 mg	721	–0.65 (0.03)	–30.7	–0.20 (0.04)	–0.27 to –0.12 p < 0.0001		
Placebo	573	–0.45 (0.03)	–23.0				

LS mean for the change from baseline in the ANOVA model with the factors treatment, study and treatment-by-study interaction as fixed effects.

total symptom score over the first 2 weeks showed similar results. Moreover, after 4 weeks of treatment, the results of reflective or snapshot TSS confirmed this greater efficacy of ebastine 20 mg (38.3% reduction from baseline) compared to loratadine 10 mg (31.7% reduction from baseline) or placebo (26.5% reduction from baseline). An interesting finding was that symptoms difficult to treat in allergic rhinitis such as nasal congestion showed significant reductions with both ebastine and loratadine treatment. The mechanism of this nasal decongestant effect is likely to be anti-inflammatory [25], but further research is required to fully understand the definitive pathway.

In conclusion, this meta-analysis confirms that ebastine 20 mg has a good efficacy profile, producing a greater decrease in mean rhinitis symptom scores from baseline than that found with loratadine 10 mg or placebo.

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