ORIGINAL ARTICLE

Effect of Bilastine Upon the Ocular Symptoms of Allergic Rhinoconjunctivitis

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■ **Abstract**

Ocular symptoms often accompany allergic rhinitis and can be as or even more bothersome for the patient than the actual nasal symptoms. Ocular manifestations of allergic rhinoconjunctivitis may result from both direct allergen-mediated mast cell stimulation on the surface of the eye and naso-ocular reflexes – histamine being one of the mediators of symptoms onset. An H_1 antihistamine would be the first line treatment for allergic conjunctivitis. Since allergic conjunctivitis is always (or almost always) accompanied by nasal symptoms, a second-generation H_1 antihistamine administered via oral route is the drug of choice for jointly managing both the nasal and the ocular symptoms – minimizing the impact of the effects inherent to first-generation H_1 antihistamine, including particularly drowsiness. Bilastine is a new H_1 antihistamine with an excellent safety profile, developed for the treatment of allergic rhinoconjunctivitis and urticaria, with potency similar to that of cetirizine and desloratadine, and superior to that of fexofenadine. This new drug has been shown to be effective in controlling the ocular symptoms of allergic rhinoconjunctivitis.

Key words: H_1 antihistamines. Bilastine. Allergic conjunctivitis. Allergic rhinoconjunctivitis.

■ **Resumen**

Los síntomas oculares acompañan en numerosas ocasiones a la rinitis alérgica y pueden ser tanto o más molestos para el paciente que los propios síntomas nasales. Los síntomas oculares de la rinoconjuntivitis alérgica pueden ser secundarios tanto por la estimulación directa de los mastocitos de la superficie ocular por parte del alérgeno como por un reflejo nasoocular, siendo la histamina uno de los mediadores protagonistas de la aparición de síntomas. Un tratamiento con antihistamínico H_1 sería el tratamiento de primera línea para la conjuntivitis alérgica. Dado que la conjuntivitis alérgica se acompaña siempre, salvo excepciones, de síntomas nasales, el antihistamínico H_1 de segunda generación por vía oral es la vía de elección al tratar de forma conjunta tanto los síntomas nasales como los oculares, minimizando el impacto de los efectos secundarios propios de los antihistamínicos H_1 de primera generación entre los que destaca la somnolencia. Bilastina es un nuevo antihistamínico H_1 con un excelente perfil de seguridad, desarrollado para el tratamiento de la rinoconjuntivitis alérgica y la urticaria con una potencia similar a la cetirizina y la desloratadina y superior a la fexofenadina, que ha demostrado ser un tratamiento eficaz para el control de los síntomas oculares de la rinoconjuntivitis alérgica.

Palabras clave: Antihistamínicos H_1. Bilastina. Conjuntivitis alérgica. Rinoconjuntivitis alérgica.

Introduction

Allergic conjunctivitis is the most frequent clinical presentation of ocular allergy, accounting for up to 98% of all cases [1]. Ocular allergy includes a group of diseases (vernal keratoconjunctivitis, atopic keratoconjunctivitis, gigantopapillary conjunctivitis, contact dermatoconjunctivitis and allergic conjunctivitis) that affect the eye surfaces (conjunctival mucosa or palpebral skin) and are commonly associated to immune-mediated inflammatory reactions of these structures [2]. In allergic conjunctivitis the underlying immune reaction is mediated by IgE antibodies. The report of the nomenclature committee of the World Health Organization (WHO) specifies that allergic conjunctivitis almost always accompanies allergic rhinitis; accordingly, it is considered more correct to refer to the condition as allergic rhinoconjunctivitis [3].

Likewise, allergic rhinitis is frequently accompanied by ocular symptoms, as a result of which the terms "rhinitis" and "rhinoconjunctivitis" are often used indistinctly.

In recent years there have been reports of important increases in the prevalence of allergic rhinoconjunctivitis, particularly in the western world. It has been estimated that between 10-25% of the general population suffers the disease, though the figures may vary according to the age of the study sample and the geographic distribution involved [4-6]. The main symptom of allergic conjunctivitis is itching, and the diagnosis should be questioned if itching is not present. Other symptoms such as tearing or lacrimation and conjunctival erythema or redness are also frequent. Some data reflecting the importance of conjunctivitis itself in patients with allergic rhinoconjunctivitis are presented below.

Data from a survey of 2500 patients with allergic rhinitis in the United States indicated that over 50% of the subjects reported eye symptoms – in the great majority of the cases involving ocular itching and tearing [7]. According to the data from a European study, out of 509 symptomatic patients with pollinic allergic rhinitis not subjected to treatment, 70% suffered conjunctivitis rated by the patient as being at least as bothersome as the rhinitis itself [8]. In another European study involving 1482 patients with allergic rhinitis, 60% reported eye symptoms and 19.7% reported eye itching and tearing as the most bothersome of the 15 symptoms evaluated in relation to rhinoconjunctivitis and comorbidities [9]. This same survey pointed out that only 46.9% of the patients presented very good conjunctivitis control, versus very good rhinitis control in 51.3% of the cases, while 12.1% and 13% of the subjects with conjunctivitis and rhinitis showed poor control, respectively, despite the treatment received. In the same study conducted in the United States with 447 patients, 54% presented eye itching and/or conjunctival erythema, and 13.6% reported eye itching and tearing as the most bothersome of all the evaluated symptoms. In turn, 54.3% and 49.7% of the subjects had very good control of conjunctivitis and rhinitis, respectively; and 5.8% and 14.8% of the patients showed very poor control of conjunctivitis and rhinitis, respectively, despite the treatment received [10]. In the setting of the allergy clinics in Spain, rhinoconjunctivitis was regarded as the first reason for consultation in the Alergológica 2005 study, representing

55.5% of the cases (2771 patients out of a total of 4991). A full 60.3% of the patients considered eye symptoms to be the main reason for seeking medical help [11].

The classification of the severity of allergic rhinoconjunctivitis according to the World Health Organization (WHO) ARIA (*Allergic Rhinitis and its Impact on Asthma*) guidelines is based on the impact of rhinitis upon patient quality of life [12]. A series of rhinitis-specific health-related quality of life (HRQoL) questionnaires have been developed, such as the RQLQ (*Rhinoconjunctivitis Quality of Life Questionnaire*) [13] or the ESPRINT-28 questionnaires, recently validated for use in Spain [14], in which a specific dimension corresponding to ocular symptoms has been included with several items – reflecting the importance of conjunctivitis per se in patients with allergic rhinoconjunctivitis. Likewise, ocular allergy-specific health-related quality of life questionnaires have been developed, such as the EAPIQ (*Eye Allergy Patient Impact Questionnaire*)[15], allowing assessment of the severity of allergic rhinoconjunctivitis according to its impact upon patient quality of life. A study of 201 patients with seasonal allergic conjunctivitis and 200 controls, carried out by ophthalmologists, in which the impact of the disease upon quality of life was assessed with the RQLQ [13], the EQ-5D (*Health questionnaire*) [16], the VFQ-25 (*Visual Functioning Questionnaire* 25) [17] and the HEDQ (*Health Economic and Demographic Questionnaire*) [18], concluded that seasonal allergic conjunctivitis significantly affected perceived health status in general, as well as patient quality of life, and even exerted a significant effect on some aspects of vision [19].

Physiopathological Mechanisms

The mechanisms underlying ocular symptoms associated to rhinitis are currently under investigation. Direct contact of the allergen with the conjunctiva, inducing an allergic response at conjunctival level parallel to nasal response and nasal-ocular reflex, appear to be the main mechanisms involved.

Local IgE response. In the same way as in the case of allergic rhinitis, the associated ocular allergic response is the result of conjunctival exposure to aeroallergens and the binding of specific IgE to mast cells at conjunctival level. Activation of mast cells induces the release of preformed inflammatory mediators such as histamine and tryptase, and of newly formed mediators such as leukotrienes, and the secretion of chemokines, cytokines and eicosanoids [20]. In recent years there have been important advances in our understanding of the physiopathology of allergic conjunctivitis. It is known that ocular mast cells are 100% tryptase- and chymase-positive (connective tissue mast cells). Chemokines ß and eotaxin-1 have been described to play an important role in mast cell activation and degranulation [21]. Conjunctival mast cells express IL-4, which contributes to polarization of the Th2 cell response, induces IgE production by B lymphocytes, induces expression of adhesion molecules [22], and together with tumor necrosis factor-alpha (TNF-α) constitutes a promoter of eotaxin expression by the corneal keratinocytes or conjunctival fibroblasts [23]. The greater or lesser presence

of local IL-10 determines a greater tendency on the part of the conjunctival mast cells to activate in response to allergens [24]. Conjunctival dendritic cells also play an important role in the pathogenesis of the disease, as a result of which their immune modulation may have an influence in relation to treatment [25,26].

Nasal-ocular reflex. Different eye structures are densely innervated by parasympathetic nerve fibers that penetrate the ocular orbit after coursing together with the parasympathetic fibers that advance towards the nasal cavity. It has been described that allergic rhinitis involves an efferent parasympathetic response at nasal level (nasal-nasal reflex) [27] and also at ocular level (nasal-ocular reflex)[28]: unilateral allergen-mediated nasal provocation can induce inflammation of the contralateral nasal fossa, in the same way that allergen stimulation at nasal level can induce a response at ocular level. The response in the contralateral fossa is inhibited by topical anticholinergic agents administered in the contralateral fossa; as a result, it is concluded that the efferent arc of the parasympathetic system is responsible for this particular reflex [29]. In the same way, an oral antihistamine is able to inhibit this reflect; as a result, it is concluded that histamine would be the afferent stimulus (or one of the stimuli) of the arc composed of the parasympathetic fibers – thereby triggering this nasal-nasal and nasal-ocular reflex [30]. Nasal corticosteroids have also been shown to be effective in treating the ocular symptoms of allergic rhinoconjunctivitis – part of this efficacy being attributed to inhibition of the nasal-ocular reflex [31,32].

The priming effect observed in allergic rhinitis (as pollinic exposure increases, the allergen response threshold decreases and the nasal inflammatory response increases)[33,34] influences enhancement of the nasal-ocular reflex. In this sense it has been speculated that this reflex is the first mechanism by which ocular symptoms appear, and that as the allergenic burden at conjunctival level increases, the eye symptoms intensify due to the local response secondary to activation of the conjunctival mast cells [31].

Independently of the different physiopathological mechanisms underlying ocular symptoms of allergic rhinoconjunctivitis, histamine is one of the main mediators involved. Its actions are not limited to triggering the signs and symptoms of the early phase of this allergic reaction but are also implicated in the release of multiple proinflammatory interleukins, with a vasoactive effect that favours arrival in the conjunctival area of a range of cellular elements that characterize allergic inflammation. Given its importance, it is logical to assume that one of the ideal approaches to the treatment of allergic conjunctivitis is the administration of antihistamines.

Topical antihistamines have been shown to be effective in allergic conjunctivitis, though oral antihistamines are also an option – and possibly even the preferential option – to be taken into account [35], since the isolated presentation of allergic conjunctivitis without rhinitis is exceptional. On the other hand, the treatment of allergic conjunctivitis with topical antihistamines has been shown to improve nasal symptoms, though with lesser efficacy than when oral antihistamines are prescribed [36-38].

Oral Antihistamines in Allergic Conjunctivitis

Second-generation oral antihistamines have been shown to be effective in providing symptoms relief and control of allergic conjunctivitis, though few studies have documented such efficacy as the main study endpoint. Most clinical studies have evaluated antihistamines in the context of rhinoconjunctivitis, in all cases adding the effects of treatment upon ocular symptoms in the analyzed symptoms scores [38].

Because of their unfavourable therapeutic index, first-generation antihistamines are not recommended as first treatment option in most cases of allergic rhinoconjunctivitis [38].

Levocetirizine has demonstrated its efficacy in application to ocular symptoms of allergic rhinoconjunctivitis in many studies involving both seasonal and perennial rhinoconjunctivitis – with significant improvements in itching and eye redness versus placebo, in both children [39,40] and in adults [41,42].

Desloratadine likewise has been shown to improve ocular symptoms in seasonal [43] and perennial allergic rhinoconjunctivitis [44] in adults. No data have been published on efficacy in children, with the exception of a non-controlled and non-randomized study [45] in which ocular symptoms were seen to disappear with desloratadine treatment.

Rupatadine has been shown to be as effective as cetirizine [46] and loratadine [47] in affording ocular symptoms relief in adult seasonal allergic rhinoconjunctivitis.

Ebastine also has been shown to be more effective than placebo or loratadine in treating eye symptoms, according to a meta-analysis involving patients diagnosed with seasonal allergic rhinoconjunctivitis [48], though in perennial rhinoconjunctivitis it only improved lacrimation – without beneficial effects upon conjunctival irritation – in the context of a 12-week survey [49]. No pediatric studies have been published on the efficacy of treatment of the ocular symptoms of the disease.

Many clinical studies have shown cetirizine to improve ocular symptoms scores versus placebo, in adult patients with both seasonal [50] and perennial allergic rhinoconjunctivitis [51], and in children [52,53].

Many studies have documented the efficacy of loratadine in treating eye symptoms of seasonal allergic rhinoconjunctivitis both in adults [54] and in children [55]. The same has been shown in application to eye symptoms of perennial allergic rhinoconjunctivitis in both adults [56] and children [57].

Fexofenadine has been seen to offer efficacy in application to the ocular symptoms of adults with seasonal allergic rhinoconjunctivitis [58] and in children diagnosed with allergic rhinitis [59].

Mizolastine likewise has been shown to offer improvement of eye symptoms of perennial and seasonal allergic rhinoconjunctivitis in adults [60,61]. No data have been published on pediatric patients, however.

Bilastine in Allergic Conjunctivitis

Bilastine is a new H_1 antihistamine developed for the treatment of allergic rhinoconjunctivitis and urticaria. Pharmacological studies have demonstrated that bilastine is highly selective for H_1 receptors [62], with antihistaminic and antiinflammatory activity [62, 63], and offering potency similar to that of cetirizine and superior to that of fexofenadine [63]. Bilastine shows rapid onset of action (within 30-60 min.) and a lasting effect (24 hours)[64]. The drug is not metabolized in the liver [65], and following absorption is mainly excreted in urine [66]. At therapeutic doses (20 mg), bilastine does not affect the central nervous system, and does not enhance the central depressant effects of alcohol [67].

The safety and efficacy of bilastine have been well established in several phase I trials involving over 600 healthy volunteers, and also in different phase II and phase III studies involving about 4000 patients with both seasonal and perennial allergic rhinitis, or with idiopathic chronic urticaria [66].

Regarding the efficacy of bilastine in treating ocular symptoms of allergic rhinoconjunctivitis, three clinical trials have been published: two were randomized, multicenter studies versus placebo and another active comparator drug in patients with seasonal allergic rhinoconjunctivitis [68,69], while the third study involved subjects with pollinic allergic rhinoconjunctivitis using the Vienna exposure chamber, comparing the efficacy of bilastine versus placebo and also

Table 1. Effect of treatment upon non-nasal symptoms score (NNSS) in patients with seasonal allergic rhinitis

Parameter	Placebo (n=245) mean (SD)	Bilastine 20 mg (n=233) mean (SD)	Desloratadine 5 mg (n=242) mean (SD)	p-value (ANOVA)
Non-nasal symptoms score AUC_{NNSS}	47.2 (35.6)	36.5 (29.8)**	37.2 (30,8)**	p<0.001
% change from baseline in the symptoms score on day 7	-24.2 (78,4)	-39.6 (47.9)**	-36.8 (54.5)*	p=0.019
% change from baseline in the symptoms score on day 14	-29.6 (69.2)	-47.1 (56.7)**	-43.7 (49.0)*	p=0.003

AUC= area under the curve of the symptoms score over the course of treatment.
Pairwise comparisons: *p<0.05 vs placebo; **p<0.01 vs placebo.

versus two active comparators [70]. The most salient aspects of the mentioned studies are commented below.

In the randomized, double-blind, multi-centre study conducted in 721 patients with seasonal allergic rhinoconjunctivitis aged between 12-70 years, treated with bilastine 20 mg, desloratadine 5 mg or placebo, and published

by Bachert et al. [68], one of the endpoints used to measure bilastine efficacy was assessment of non-nasal symptoms score (NNSS), including ocular manifestations (itching, redness, foreign body sensation and tearing) and the rhinitis quality of life questionnaire (RQLQ), which includes a domain specific of eye symptoms. The patients treated both with bilastine and with

Table 2. Area under the curve of individual ocular symptoms score over the course of treatment, in patients with seasonal allergic rhinitis.

Symptom	Parameter	Placebo (n=245) Mean (SD)	Bilastine 20 mg (n=233) Mean (SD)	Desloratadine 5 mg (n=242) Mean (SD)	p-value (ANOVA)
Ocular itching	AUC	14.2 (10.8)	11.6 (9.6)*	12.0 (9.7)*	p=0.0116
	AUCadj	-10.1 (10.5)	-12.4 (10.2)**	-13.6 (11.1)**	p=0.0012
Tearing	AUC	10.5 (9.8)	8.0 (8.1)**	8.6 (8.4)*	p=0.0048
	AUCadj	-9.2 (10.4)	-11.0 (9.6)	-11.8 (11.5)*	p=0.0277
Conjunctival redness	AUC	10.7 (10.2)	9.0 (8.7)**	8.6 (9.2)**	p=0.0349
	AUCadj	-8.5 (10.5)	-11.2 (10.2)*	-10.7 (10.3)*	p=0.0081

AUC= area under the curve of the symptom score over the course of treatment.
AUCadj= area under the curve of the change from baseline in the score of each symptom.
Pairwise comparisons: *p<0.05 vs placebo; **p<0.01 vs. placebo.

Table 3. Percentage change from baseline in the individual ocular symptoms score on day 7 and day 14 of treatment, in patients with seasonal allergic rhinitis.

Parameter	Placebo (n=225)	Bilastine 20 mg (n=226)	Cetirizine 10 mg (n=227)	p-value (ANOVA)
	mean (SD)	mean (SD)	mean (SD)	
% change in eye itching				
Day 7	-24.4 (63.1)	-49.6 (51.2)***	-48.5 (57.5)***	p<0.001
Day 14	-41.2 (57.8)	-64.4 (46.6)***	-59.1 (54.1)***	p<0.001
% change in tearing				
Day 7	47.2 (35.6)	36.5 (29.8)***	37.2 (30.8)***	p<0.001
Day 14	-24.2 (78.4)	-39.6 (47.9)***	-36.8 (54.5)***	p=0.002
% change in conjunctival redness				
Day 7	-33.6 (61.1)	-60.0 (51.4)***	-53.4 (53.4)***	p<0.001
Day 14	-56.3 (51.2)	-65.2 (50.8)	-65.3 (50.9)	NS

Pairwise comparisons: ***p<0.001 vs placebo.

desloratadine showed statistically significant improvement in non-nasal symptoms versus placebo, according to the efficacy endpoint defined as the area under the curve of the symptoms score and the percentage change in non-nasal symptoms score on day 7 and day 14 with respect to the baseline visit (Table 1). When analyzing the data related to the ocular manifestations of non-nasal symptoms, bilastine and desloratadine continued to be more effective than placebo (data not published, obtained from the manufacturer; Table 2). Likewise, bilastine proved more effective than placebo (p = 0.011) in improving the score of the domain corresponding to the ocular symptoms of the RQLQ (bilastine -1.6 (1.6); placebo -1.2 (1.6)).

In the randomized, double-blind, multi-centre study conducted in 683 patients with seasonal allergic rhinoconjunctivitis aged between 12-70 years, treated with bilastine 20 mg, cetirizine 10 mg or placebo, and published by Kuna et al. [69], one of the efficacy endpoints was the assessment of non-nasal symptoms, specifically eye itching, conjunctival redness and tearing. In the analysis of results relating to eye symptoms, in which the effect of treatment was measured as the percentage change in individual symptoms score on day 7 and day 14 of treatment versus baseline, both bilastine and cetirizine were seen to be more effective than placebo in reducing itching, conjunctival redness and tearing – with the exception of conjunctival erythema on day 14 of treatment, where although both bilastine and cetirizine were more effective than placebo, statistical significance was not reached (Table 3). When evaluating the area under the curve (AUC) of the instantaneous and reflexive ocular symptoms score over the 14 days of treatment as efficacy endpoint, bilastine and cetirizine were seen to be significantly more effective than placebo both globally (Table 4) and on considering the individual symptoms (data not published and obtained from the manufacturer) (Table 5).

Using a standardized pollen exposure provocation test (the Vienna chamber) in 75 patients with pollinic allergic rhinoconjunctivitis aged between 18-55 years, Horak et al. [70] showed bilastine, fexofenadine and cetirizine to be more effective than placebo (p < 0.03) in improving the evaluated ocular symptoms (itching, redness and tearing) one hour after antihistamine administration: the mean ocular symptoms score

Table 4. Effect of two weeks of treatment upon non-nasal symptoms score (NNSS) as assessed by patients with seasonal allergic rhinitis

Parameter	Placebo (n=225)	Bilastine 20 mg (n=226)	Cetirizine 10 mg (n=227)	p-value (ANOVA)
	mean (SD)	mean (SD)	mean (SD)	
AUC$_{NNSS}$				
Reflexive symptoms	31.02 (24.7)	21.79 (21.8)***	22.19 (22.5)***	p<0.001
Instantaneous symptoms	32.89 (25.9)	23.46 (21.7)***	23.73 (22.8)***	p<0.001
Change in NNSS from baseline	-0.91 (1.90)	-1.65 (1.89)***	-1.76 (2.03)***	p<0.001
95% CI	-1.16; -0.66	-1.89; -1.40	-2.02; -1.49	

AUC= area under the curve of the symptoms score over the duration of treatment.
Pairwise comparisons: ***p<0.001 vs placebo.

Table 5. Effect of two weeks of treatment upon the score of each of the ocular symptoms (reflexive and instantaneous) in patients with seasonal allergic rhinitis

	Parameter	Placebo (n=225)	Bilastine 20 mg (n=226)	Cetirizine 10 mg (n=227)	p-value (ANOVA)
		Mean (SD)	Mean (SD)	Mean (SD)	
Reflexive symptoms					
Eye itching	AUC	12.0 (8.7)	8.7 (7.8)[**]	8.7 (8.3)[**]	p<0.001
	AUCadj	-4.8 (8.7)	-8.7 (8.8)[**]	-8.7 (9.3)[**]	p<0.001
Tearing	AUC	9.1 (8.6)	6.3 (7.7)[**]	6.2 (7.8)[**]	p<0.001
	AUCadj	-4.4 (8.9)	-7.1 (8.9)[**]	-7.8 (9.4)[**]	p<0.001
Conjunctival redness	AUC	9.9 (9.3)	6.8 (7.8)[**]	7.3 (8.3)[**]	p<0.001
	AUCadj	-3.9 (8.7)	-7.1 (9.2)[**]	-7.6 (8.8)[**]	p<0.001
Instantaneous symptoms					
Eye itching	AUC	12.7 (9.0)	9.5 (7.8)[**]	9.3 (8.5)[**]	p<0.001
	AUCadj	-5.2 (9.1)	-8.9 (9.5)[**]	-8.9 (9.4)[**]	p<0.001
Tearing	AUC	9.7 (9.0)	6.8 (7.7)[**]	6.7 (7.9)[**]	p<0.001
	AUCadj	-4.6 (9.0)	-7.2 (9.2)[**]	-8.0 (9.4)[**]	p<0.001
Conjunctival redness	AUC	10.6 (9.7)	7.2 (8.0)[**]	8.0 (9.4)[**]	p<0.001
	AUCadj	-4.2 (9.1)	-7.7 (9.5)[**]	-7.7 (9.2)[**]	p<0.001

AUC= area under the curve of the symptom score over the course of treatment.
AUCadj= area under the curve of the change from baseline in the score of each symptom.
Pairwise comparisons: [**]p<0.01 vs placebo.
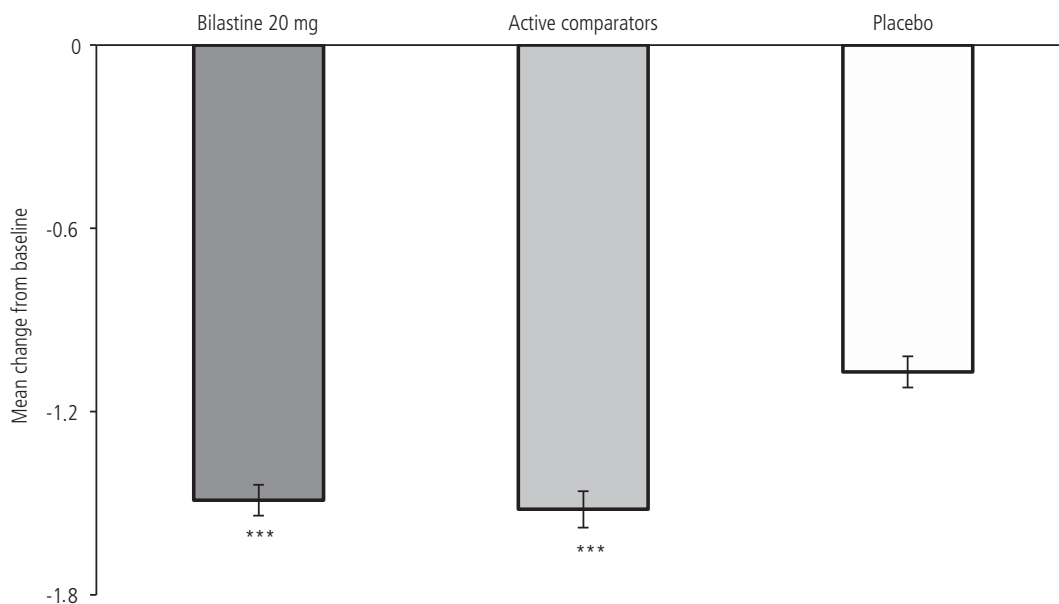
Figure 1. Mean change from baseline in ocular symptoms score (mean±SEM) during the observation period, in patients with seasonal allergic rhinitis treated for 14 days with bilastine 20 mg, placebo or another active comparator drug.
[**]p<0.001 vs placebo.

(mean ± standard error of the mean) for placebo and bilastine was 0.95±0.11 and 0.74±0.09, respectively. In addition, bilastine was seen to offer lasting protection in relation to eye symptoms – statistical significance (p<0.03) being recorded 26 hours after administration of the drug: the ocular symptoms score for placebo and bilastine was 1.05±0.11 and 0.80±0.11, respectively. Ceterizine also showed this prospective effect after 26 hours, but no so fexofenadine.

To date, 7 phase II and phase III trials have been carried out with bilastine in patients with seasonal or perennial allergic
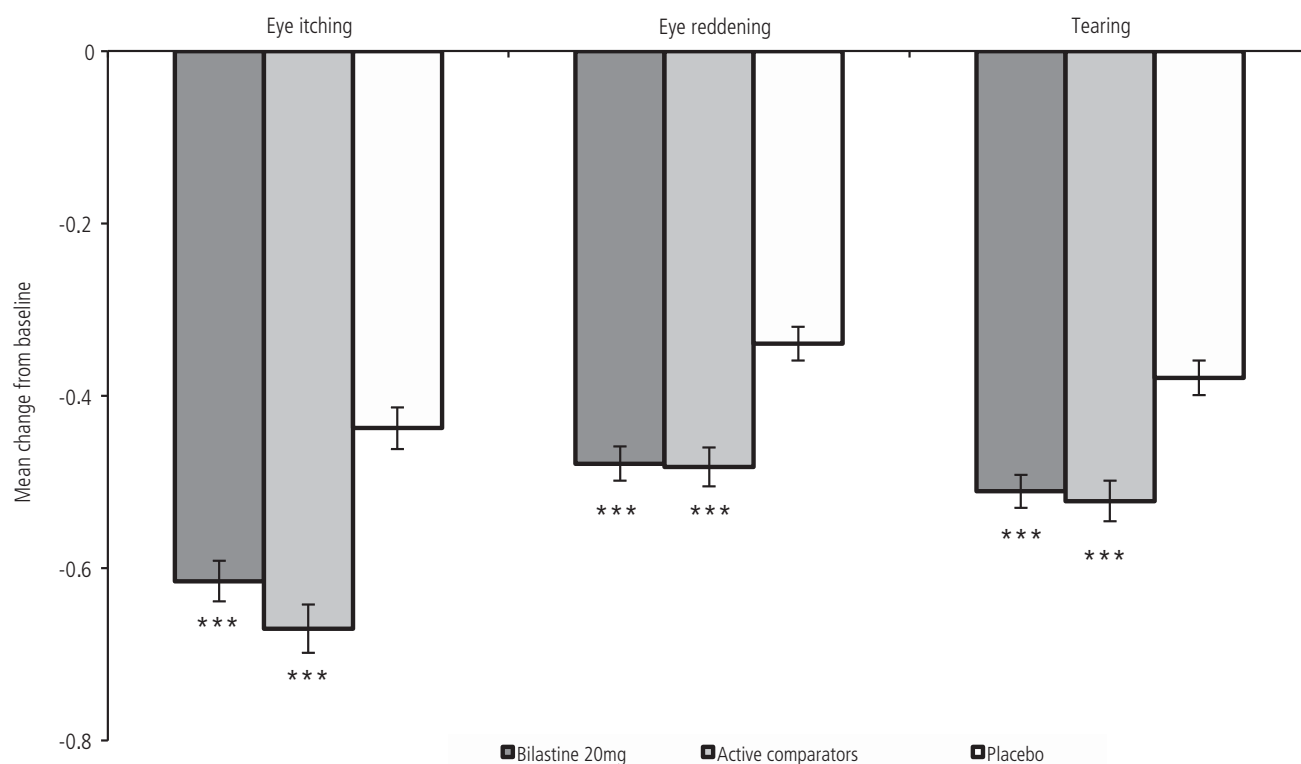
Figure 2. Effect of treatment for two weeks on the mean change in individual ocular symptoms score from baseline (mean±SEM) during the observation period, in patients with seasonal allergic rhinitis.
***p<0.001 vs placebo.

rhinoconjunctivitis, encompassing a total of 3846 patients, of which 1114 were treated with bilastine, 1109 with placebo, and 923 with an active comparator drug (desloratadine 5 mg in 242 subjects and cetirizine 10 mg in 681 patients) ([66]. The global analysis of the results from the 7 studies must be interpreted considering the limitations implied by including data from studies in different phases (phases II and III), with different treatment indications (seasonal and perennial allergic rhinoconjunctivitis), different active comparators (cetirizine and desloratadine), and different durations (14 and 28 days). The analysis of the global data on the effect of treatment referred to the overall ocular symptoms (itching, redness and tearing) showed bilastine and the rest of the active comparator drugs to be more effective than placebo in terms of the mean change in ocular symptoms score from baseline (data not published, and obtained from the manufacturer) (Figure 1). When analyzing ocular manifestations individually, bilastine and the active comparators were seen to be more effective than placebo in application to all three of the evaluated symptoms (data not published, obtained from the manufacturer) (Figure 2) – with no differences between bilastine and the active comparators.

In conclusion, bilastine is a new H$_1$ antihistamine with an excellent safety profile, indicated for the treatment of allergic rhinoconjunctivitis, and which has been shown to be effective in controlling ocular symptoms.

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Conflicts of interest

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