Allergic Conjunctivitis and H_1 Antihistamines

A del Cuvillo,[1] J Sastre,[2,3] J Montoro,[4] I Jáuregui,[5] I Dávila,[6] M Ferrer,[7] J Bartra,[8,3] J Mullol,[9,3] A Valero[8,3]

[1] Clínica Dr. Lobatón, Cádiz, Spain
[2] Servicio de Alergia, Fundación Jiménez Díaz, Madrid, Spain
[3] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES)
[4] Unidad de Alergia, Hospital La Plana, Villarreal (Castellón), Spain
[5] Servicio de Alergología, Hospital de Basurto, Bilbao, Spain
[6] Servicio de Inmunoalergia, Hospital Universitario, Salamanca, Spain
[7] Departamento de Alergia e Inmunología Clínica, Clínica Universidad de Navarra, Pamplona, Spain
[8] Unitat d'Al·lèrgia, Servei de Pneumologia i Al·lèrgia Respiratòria, Hospital Clinic (ICT), Barcelona, Spain
[9] Unitat de Rinologia & Clínica de l'Olfacte, Servei d'Oto-rino-laringologia, Hospital Clínic Immunoal·lèrgia Respiratòria Clínica i Experimental, IDIBAPS. Barcelona, Spain

Abstract

Allergic conjunctivitis is the most common form of ophthalmological allergy. Eye symptoms are one of the main and most frequent reasons for consultation among patients with allergic rhinoconjunctivitis, which in turn is the most common reason for visiting the allergologist, according to the Alergológica 2005 study. Itching is the key symptom of allergic conjunctivitis, and its relief is the principal objective of the broad range of treatment options available. Topical antihistamines with multiple actions (mast cell stabilization, and antiinflammatory and antihistaminic actions) are probably the best treatment option, thanks to their rapid action, safety and convenience of use. However, oral antihistamines (preferentially second generation drugs) can also play an important role, since they are of established efficacy and offer adequate treatment of the nasal symptoms that tend to accompany the ocular manifestations of allergic rhinoconjunctivitis. Models of allergic conjunctivitis are useful for investigational purposes and for advancing our knowledge of allergic reactions. Advances in the study of the physiopathology of ocular allergy allow us to introduce new therapeutic options for the management of such allergic reactions, thanks to the findings derived from models of this kind. The present review provides an update to the published data on allergic conjunctivitis and the current role of both topical and ocular antihistamines in treating the disorder.

Key words: Allergic conjunctivitis, topical antihistamines, oral antihistamines, ocular allergy.

Resumen

Las conjuntivitis alérgicas son el cuadro más prevalente dentro de las alergias oculares. Los síntomas oculares son uno de los motivos principales y más frecuentes de consulta en los pacientes con rinoconjuntivitis alérgica, que es a su vez la causa más común de visita al alergólogo, según el estudio Alergológica 2005. El prurito es el síntoma clave de las conjuntivitis alérgicas y su alivio es el objetivo principal de las múltiples opciones terapéuticas disponibles. Los antihistamínicos tópicos con acción múltiple (estabilizadora del mastocito, antiinflamatoria y antihistamínica), son probablemente la mejor opción terapéutica debido a su rapidez de acción, seguridad y comodidad de uso, pero los antihistamínicos orales, preferiblemente los de segunda generación, pueden tener un papel importante, dada su eficacia demostrada y dado que actúan de forma efectiva sobre los síntomas nasales, que suelen acompañar a los oculares en las rinoconjuntivitis alérgicas. El modelo de investigación de la conjuntivitis alérgica es un interesante patrón en la experimentación y avance del conocimiento de las reacciones alérgicas. Los avances en el estudio de la patofisiología de la alergia ocular permiten introducir nuevas opciones terapéuticas para el manejo de estas reacciones alérgicas gracias a los hallazgos realizados sobre este modelo. En esta revisión se hace una actualización de los datos publicados sobre conjuntivitis alérgica y el papel que los antihistamínicos, tanto tópicos como oculares, tienen en su tratamiento actualmente.

Palabras clave: Conjuntivitis alérgica. Antihistamínicos tópicos. Antihistamínicos orales. Alergia ocular.

Introduction

Ocular allergy includes a group of diseases that affect the eye surfaces (conjunctival mucosa or palpebral skin) and are commonly associated to immune-mediated inflammatory reactions of these structures. Allergic conjunctivitis is the most common clinical form of ocular allergy, and the underlying immune reaction tends to be mediated by IgE. In the report of the nomenclature review committee of the World Allergy Organization [1], IgE-mediated allergic conjunctivitis is specified as being commonly associated to allergic rhinitis. As a result, the term "allergic rhinoconjunctivitis" is considered to be more correct in reference to the disease.

There are few epidemiological data on allergic conjunctivitis, probably because of the lack of classification criteria, underdiagnosis of the condition, and the fact that the disease is often associated to allergic rhinitis, which draws scant attention. The prevalence of ocular allergy is high, and although few studies have specifically addressed its incidence, eye involvement data are commonly mentioned in allergic diseases publications.

In the Alergológica 2005 study [2], allergic rhinoconjunctivitis was found to be the main reason for consulting the allergologist, with 55.5% of all cases. In turn, 15.3% of the patients consulting for allergic rhinoconjunctivitis already had a history of allergic conjunctivitis. A full 60.3% of the patients considered the eye symptoms to be one of the main reason for seeking medical help.

Agreement regarding the classification of ocular allergies is limited. Syndromically, a distinction can be made between mild presentations (acute, seasonal and perennial according to the time of exposure to the allergen) and more serious conditions such as vernal or spring keratoconjunctivitis, atopic keratoconjunctivitis, giant papillary conjunctivitis and contact dermatoconjunctivitis [3]. Acute, seasonal and perennial allergic conjunctivitis are represented by localized inflammatory processes affecting the conjunctiva of one or both eyes. These conditions develop suddenly (acute forms) or according to the time of exposure: seasonal (outdoor allergens) or perennial (indoor allergens). Vernal keratoconjunctivitis is a bilateral inflammation of the palpebral and bulbar conjunctiva, and of the cornea. The underlying cause is not known, and the more serious cases can lead to blindness. Atopic keratoconjunctivitis is the term used in reference to the global ocular manifestations of atopic dermatitis. The condition can prove serious on affecting the cornea and may cause blindness. Giant papillary conjunctivitis is distinct from all the other conditions and is characterized by the formation of giant conjunctival papillae as a reaction to trauma or friction (the condition being initially described in contact lens wearers). Contact dermatoconjunctivitis in turn consists of contact dermatitis affecting the palpebral skin. Figures 1, 2, 3, 4 and 5 show different clinical aspects of these diseases.

The prevalences of the different forms of ocular allergy have not been well established, though the serious forms are believed to represent only 2% of all eye allergies. Nevertheless, their seriousness makes it necessary to take these forms into account. In contrast, mild allergic conjunctivitis (acute, seasonal, perennial) is much more common, representing up to

Figure 1. Acute allergic conjunctivitis (cheimosis).

Figure 2. Allergic conjunctivitis.

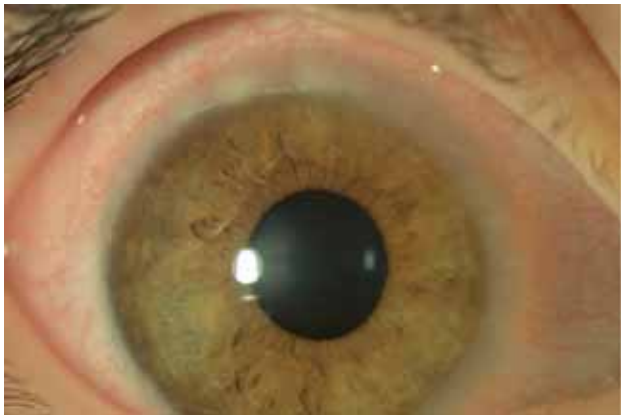

Figure 3. Limbal vernal keratoconjunctivitis.

Figure 4. Tarsal vernal keratoconjunctivitis.

Figure 5. Contact dermatoconjunctivitis.

98% of all cases of ocular allergy, and its incidence moreover is increasing [4].

The main symptom of allergic conjunctivitis is itching. Indeed, in the absence of such itching, the diagnosis should be questioned. Other symptoms such as lacrimation (tearing), red eye, foreign body sensation and edema (swelling) are also very frequent. Other data suggestive of allergic conjunctivitis are the coincidence of the condition with symptoms of rhinitis and asthma.

The diagnosis of allergic conjunctivitis is fundamentally clinical, and is based on a concordant case history. However, it is important to confirm the IgE-mediated pathogenic mechanism by means of allergy tests or the determination of specific IgE in serum, in order to identify the causal allergen and thus adopt preventive measures against it. Identification of the causal allergen makes it possible to classify allergic conjunctivitis as seasonal (involving outdoor allergens such as pollen and fungi) or perennial (involving indoor allergens such as dust mites, insects or fungal species).

The pathogenesis of ocular allergy is complex and multifactorial, and can be regarded as the result of environmental interaction with a group of predisposing genes. Few studies have explored the genetic associations of allergic conjunctivitis, though a clear familial predisposition to develop the disease has been demonstrated [5]. An association has been found between allergic conjunctivitis and chromosomes 5, 16 and 17, and also chromosome 6 when considering specific allergens. This suggests that there may be organ-specific susceptibility genes in allergic diseases, since the genes identified for conjunctivitis differ from those established for atopic asthma [6]. In recent years there have been important advances in our knowledge of the physiopathology of ocular allergy. In this context, it has been suggested that there may be genetically conditioned differences in local IL-10 levels, determining an increased tendency on the part of conjunctival mast cells to become activated by allergens [7]. A number of studies have also stressed the importance of the conjunctival dendritic cells in the pathogenesis of the disease, and have reported that immune modulation of such cells may play a role in the treatment of the disorder [8, 9]. Mast cell activation and degranulation have also been studied in depth in recent years, with descriptions of the important role of the ß-chemokines not only in recruiting leukocytes but also in mast cell priming and activation. In addition, eotaxin-1 has been shown to play a key role as co-stimulating signal in conjunctival mast cells [10]. A model of allergic conjunctivitis has been used to show that an eotaxin-1 receptor antagonist is able to inhibit both immediate and delayed allergic reactions, thus defining this mechanism as a very interesting therapeutic target in allergic reactions [11]. All these improvements in our knowledge of ocular allergy have allowed tremendous advances in the proposition of new therapeutic options for the control of allergic reactions, since the allergic conjunctivitis model is simple and easily reproducible.

The usual treatment of allergic conjunctivitis comprises nonspecific measures such as the application of cold dressings, artificial tears and the avoidance of allergens. However, these measures are typically ineffective or not very practical, and pharmacological treatment normally proves necessary. Since the conjunctiva is an accessible mucosa, topical drug application logically appears as the ideal approach for the treatment of allergic conjunctivitis, since rapid action is assured, with improvement in eye hydration. Many studies have shown this administration route to be equally or even more effective than oral or nasal topical treatments [12, 13].

Several drug groups have been proposed for the treatment of allergic conjunctivitis. Drugs with antiallergic action – simply antihistaminic or multiple (mast cell stabilization, eosinophil blocking or with added antiinflammatory action) – are the most important substances, though use is also made of topical vasoconstrictors, which are very active in relation to the patient symptoms but have adverse effects (glaucoma, rebound effects, conjunctival irritation and hypersensitivity). Topically applied nonsteroidal antiinflammatory drugs (NSAIDs) are also

recommended, as they have been shown to be effective and produce few side effects. Alternatively, topical ocular corticoids are very effective (probably the most effective of all options), but pose the important risk of frequent side effects (glaucoma, cataracts, corneal ulcers) [3].

Oral antihistamines are also a treatment option to be taken into account, particularly when considering that the isolated presentation of allergic conjunctivitis without associated rhinitis is rare. Furthermore, although the topical treatment of allergic conjunctivitis has been shown to improve the nasal symptoms of allergic rhinoconjunctivitis, systemic antihistamines are more potent in securing relief from symptoms of this kind [13]. However, some studies have demonstrated an adverse effect on the part of oral antihistamines, causing dry eye, compared with topical antihistamines, which do not produce this effect [14].

The most severe forms of ocular allergy (vernal keratoconjunctivitis and atopic keratoconjunctivitis on one hand, and contact dermatoconjunctivitis on the other) are chronic allergic disorders with physiopathogenic mechanisms that are more complex than in the case of allergic conjunctivitis. As a result, the role of antihistamines (both oral and topical) is very limited in such situations, and is confined to attempting control of the most bothersome clinical manifestations (especially itching) during the symptomatic periods. In this context, the most effective treatment is currently topical corticoid use [3].

The present review affords an update on the existing scientific evidence relating to the efficacy of treatment of the most frequent forms of ocular allergy (allergic conjunctivitis) using oral as well as topical antihistamines.

Topical antihistamines in allergic conjunctivitis

Many clinical studies have documented the efficacy of topical antihistamines in the management of allergic conjunctivitis; indeed, these drugs are currently the treatment of choice for this disorder.

Histamine is one of the mediators released by mast cells after specific allergen binding to the IgE presented on the cell surface. This mediator is the main contributor to the signs and symptoms of the immediate reaction characterizing allergic conjunctivitis. As a result, drugs that antagonize histamine action play an important role in terms of symptoms relief.

The most widely used first generation ocular topical antihistamines are antazoline (0.05%) and pheniramine; these drugs are usually administered in combination with vasoconstrictors to improve efficacy in providing allergic conjunctivitis symptoms relief. A study has been published [15] comparing the efficacy of prophylactic treatment with pheniramine versus olopatadine in allergic rhinoconjunctivitis. The conclusion was that both drugs are superior to placebo, and that pheniramine is more effective than olopatadine when administered prior to conjunctival provocation. However, even though the affinity of certain first generation antihistamines is greater than that of levocabastine (a second generation drug) for example, it has not been possible to demonstrate that they moreover offer some antiinflammatory-antiallergic action in addition to their antipruriginous effects – in contrast to the second generation antihistamines at therapeutic doses.

Levocabastine was the first second generation ocular topical antihistamine indicated for the treatment of allergic conjunctivitis [16]. This substance was followed by many other drugs with antihistaminic actions and some added antiinflammatory properties (emedastine [17], azelastine [18]), and which outperformed classical disodium cromoglycate and nedocromil in a number of aspects, particularly as refers to onset of action, convenience of use (less frequent administration), and potency of effect.

The introduction in the pharmacopoeia of drugs with dual action, i.e., antihistaminic effects plus mast cell membrane stabilization properties, has constituted an important step forward in the management of allergic conjunctivitis. In this setting, ketotifen is a mast cell stabilizer with inhibitory effects upon the release of inflammatory mediators that has been shown to offer great efficacy in controlling the symptoms of allergic conjunctivitis, even outperforming levocabastine [19]. It is the only drug available in unit dose form without preservatives – thus making it ideal for contact lens wearers. Olopatadine in turn possesses dual action, as demonstrated by many studies that have confirmed its efficacy in the treatment of allergic conjunctivitis [20]. Although this drug contains a preservative (benzalkonium chloride), it has been successfully used to treat allergic reactions in patients wearing contact lenses, without having to suppress its administration [21].

The efficacy and safety of the topical antihistamines in application to allergic conjunctivitis have been evaluated by a metaanalysis published in the year 2004 [22], comprising 9 randomized, placebo-controlled and double-blind studies (some involving a cross-over design and others not), that met the required scientific quality and methodological design specifications. The conclusion was that most studies reflect improvement in the symptoms of allergic conjunctivitis following provocation testing, particularly as refers to the main symptom (itching). There was no evidence of the superiority of one topical antihistamine over the others in this metaanalysis. However, no formal metaanalysis proved possible, since most of the studies failed to tabulate the mean scores of the analyzed variables with their corresponding associated error, and some studies moreover did not specify the p-value obtained – thus making it impossible to establish the degree of benefit obtained from the treatment.

This same metaanalysis established a comparison between the efficacy of treatment of allergic conjunctivitis with topical antihistamines and with topical mast cell stabilizers, selecting 8 studies that met the requirements (masked and randomized designs). An evaluation was made of 6 studies that assessed the effects of longer term therapy – no significant differences being recorded in favor of any of the interventions. In the short term studies (normally after conjunctival provocation with allergen), a significant difference was observed in favor of the topical antihistamines. In this sense, the patients that used levocabastine perceived a beneficial effect of treatment that was 1.3-fold greater than with the mast cell stabilizers (cromoglycate or nedocromil) – though the corresponding odds ratio (OR) failed to reach statistical significance. The authors

finally concluded that there is limited evidence suggesting that the topical antihistamines may afford a faster therapeutic effect than the topical mast cell stabilizers, and that both are effective compared with placebo. No relevant adverse effects were recorded with any of the treatments analyzed.

Since the publication of this metaanalysis, there have been many studies confirming the efficacy of the different existing topical antihistamines versus placebo and also versus each other – underscoring the therapeutic benefits added to histamine receptor antagonism, and the dual action of these treatment agents.

The topical antihistamines emedastine and ketotifen have been compared based on the model of allergic conjunctivitis provocation with allergen – no significant differences being recorded in terms of ocular itching relief. Both drugs were shown to be significantly more effective than placebo [23]. Based on this same model, olopatadine has been shown to be more effective than topical azelastine in affording itching relief in allergic conjunctivitis [24].

A clinical study compared the efficacy of topical olopatadine and ketotifen in affording relief from the symptoms of allergic conjunctivitis during 15 days of follow-up [25]. The conclusion was that olopatadine is more effective than ketotifen, though the authors did not inform of the randomized study design, and the statistical significance of the recorded difference was not stated. Consequently, the mentioned difference cannot be taken to represent firm evidence. In fact, this same study was repeated on a randomized and masked basis, concluding that there were no significant differences between the two topical treatments – though significant superiority versus placebo (artificial tears) was documented both clinically and in terms of the inflammation markers [26]. Another study established masked comparison of these same topical antihistamines, as refers to patient preference. The authors concluded that a significantly greater proportion of patients preferred olopatadine versus ketotifen in terms of efficacy and convenience of use [27].

A comparison also has been made of olopatadine versus epinastine (both as topical solutions), based on the model of conjunctival provocation with allergen. In this randomized, masked and contralaterally controlled study, olopatadine was found to be more effective than epinastine in affording itching relief and in dealing with reddening of the eye in allergic conjunctivitis [28]. Based on this same model and design, olopatadine has been shown to offer better control of itching and red eye than levocabastine, with less discomfort after topical application [29].

The topical antihistamines emedastine and levocabastine have also been compared as refers to efficacy in preventing and treating allergic conjunctivitis – the conclusion being that both treatments are significantly more effective than placebo, and that emedastine is more effective than levocabastine in adults and children over four years of age [30].

A recently published metaanalysis [31] concludes that topical nonsteroidal antiinflammatory drugs (NSAIDs) are more effective than placebo in providing relief from the main symptom (itching) and main sign (reddening of the eye) of allergic conjunctivitis, though mention is made of the need for comparative studies versus topical antihistamines/mast cell stabilizers, in order to establish the role of NSAIDs in the management of allergic conjunctivitis. In a study comparing efficacy in terms of itching and red eye relief with topical emedastine versus topical ketorolac in the model of conjunctival provocation with allergen, emedastine was seen to be significantly superior to the NSAID [32]. This same result was repeated on comparing olopatadine versus ketorolac [33], thereby partially answering the question raised by the above mentioned metaanalysis.

In conclusion, topical antihistamines – preferably those with established dual action – are very effective in treating allergic conjunctivitis, and outperform other groups of drugs such as mast cell stabilizers or topical NSAIDs. Table 1 presents the most relevant data in relation to the use of topical antihistamines for the treatment of allergic conjunctivitis.

Table 1. Topical antihistamines in allergic conjunctivitis

Drug	Dose	Other actions	Comparative studies
Azelastine	/12 h	Inhibits leukotrienes, reduces ICAM-1 expression. Dual action	< olopatadine
Levocabastine	/6 h		< emedastine < olopatadine
Emedastine	/12 h		> levocabastine
Olopatadine 0.01% 0.02%	 /12 h /24 h	Dual action: antiH1 + mast cell stabilizer	> epinastine > levocabastine > ketotifen > azelastine
Epinastine	/12 h	Dual action: antiH1 + mast cell stabilizer	< olopatadine
Ketotifen	/12 h.	Dual action: antiH1 + mast cell stabilizer	< olopatadine

Oral antihistamines in allergic conjunctivitis

Histamine is one of the main mediators of allergic reactions occurring as a result of contact between the allergen and the conjunctival mucosa. Its actions are not limited to triggering of the signs and symptoms of the early phase of the allergic reaction but are also implicated in the release of multiple proinflammatory cytokines, with a vasoactive effect that favors arrival in the conjunctival zone of a range of cellular elements that characterize allergic inflammation.

The antihistamines exert a number of effects upon the histamine receptor. On one hand, it is now clear that all known antihistamines act as reverse agonists, inactivating the intracellular actions of the receptor. On the other hand, antiinflammatory effects have been demonstrated for these drugs, explained by modulation of nuclear factor NF-κB, such as the inhibition of ICAM-1 expression or action upon the bradykinins [34].

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

Because of their unfavorable therapeutic index, the first generation antihistamines are not recommended as first treatment option in most cases of allergic rhinoconjunctivitis [35].

Most second generation antihistamines have demonstrated efficacy in the joint control of the nasal and ocular symptoms of allergic rhinoconjunctivitis. As a result, and since the ocular and nasal symptoms tend to coexist, these drugs are always a first treatment option. Topical antihistamines have also been found to exert an effect upon the nasal symptoms [12, 13], explained mainly by nasal exposure to the medication as a result of lacrimonasal duct drainage. However, this effect upon the nasal symptoms is not as potent as in the case of antihistamines administered via the oral route.

Levocetirizine has demonstrated its efficacy in application to the ocular manifestations of allergic rhinoconjunctivitis in many studies involving both seasonal and perennial rhinoconjunctivitis – with significant improvements in itching and red eye versus placebo, in both children [36, 37] and in adults [38, 39].

Desloratadine likewise has been shown to improve the ocular symptoms in seasonal [40] and perennial allergic rhinoconjunctivitis [41] adults. No data have been published on efficacy in children, with the exception of a non-controlled and non-randomized study [42] in which the ocular symptoms were seen to disappear with desloratadine treatment.

Rupatadine has been shown to be as effective as cetirizine [43] and loratadine [44] 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 the eye symptoms, according to a metaanalysis involving patients diagnosed with seasonal allergic rhinoconjunctivitis [45], though in perennial rhinoconjunctivitis it only improved lacrimation – without beneficial effects upon conjunctival irritation – in the context of a 12-week survey [46]. 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 the ocular symptoms scores versus placebo, in adult patients with both seasonal [47] and perennial allergic rhinoconjunctivitis [48], and in children [49, 50].

Many studies have documented the efficacy of loratadine in treating the eye symptoms of seasonal allergic rhinoconjunctivitis in both adults [51] and in children [52]. The same has been shown in application to the eye symptoms of perennial allergic rhinoconjunctivitis in both adults [53] and children [54].

Fexofenadine has been seen to offer efficacy in application to the ocular manifestations of adults with seasonal allergic rhinoconjunctivitis [55] and in children diagnosed with allergic rhinitis [56].

Mizolastine likewise has been shown to offer improvement of the eye symptoms of perennial and seasonal allergic rhinoconjunctivitis in adults [57, 58]. No data have been published on pediatric patients, however.

Table 2. Oral antihistamines in allergic rhinoconjunctivitis

Drug	Adults PARC	Adults SARC	Children PARC	Children SARC	Observations
Levocetirizine	Yes	Yes	Yes	Yes	
Desloratadine	Yes	Yes	No	No	Metaanalysis
Rupatadine	Yes	Yes	No	No	
Ebastine	Yes	Yes	No	No	Metaanalysis
Cetirizine	Yes	Yes	Yes	Yes	
Loratadine	Yes	Yes	Yes	Yes	
Fexofenadine	Yes	Yes	Yes	Yes	
Mizolastine	Yes	Yes	No	No	

PARC: Perennial allergic rhinoconjunctivitis; SARC: Seasonal allergic rhinoconjunctivitis.

Table 2 presents the most relevant data in relation to the use of oral antihistamines for the treatment of allergic conjunctivitis.

In conclusion, the great majority of the oral antihistamines currently in use have been shown to be useful, with the maximum level of scientific evidence, in affording relief from the ocular manifestations of allergic rhinoconjunctivitis. The choice of treatment should be established on an individualized basis, taking into account the age of the patient, the predominant clinical picture (nasal or ocular symptoms, or both), the patient preferences and the coexisting illnesses, to name but a few. These factors will help define ideal treatment, based on the existing scientific evidence, and which we have attempted to describe in this review.

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Alfonso del Cuvillo

Clínica Dr. Lobatón
Avenida Fernández Ladreda nº 9
Cádiz 11008
Spain
E-mail: dr.cuvillo@comcadiz.es

