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ORIGINAL RESEARCH

Bilastine for the treatment of allergic rhinoconjunctivitis and urticaria: results from an international Delphi study

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Abstract

Background: Second-generation oral H_1-antihistamines, including bilastine, represent the emerging treatments of allergic rhinitis (including rhinoconjunctivitis) and chronic urticaria in both adults and children. This study analyses available evidence supporting the use of bilastine amongst second-generation antihistamines for the symptomatic treatment of allergic rhinitis and urticaria in adults and children.

Methods: Consensus amongst experts from 17 countries on the ideal treatment of rhinitis and urticaria, and the specific role of bilastine was measured by means of a modified Delphi process. A total of 12 statements were voted on by the experts using a five-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = undecided; 4 = agree; 5 = strongly agree). The definition of consensus was set at a minimum of 80% concordance for 4+5 scores (agree or strongly agree).

Results: All proposed statements reached consensus, with a concordance of ≥98% for five statements and ≥96% for seven.

Conclusions: The wide consensus obtained for the proposed statements suggests a prominent role for bilastine in the management of allergic rhinitis and urticaria.

Keywords: antihistamines, allergic rhinitis, allergic rhinoconjunctivitis, allergy, urticaria, bilastine, Delphi process.

Citation

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Introduction

Allergic rhinitis (also referred to as rhinoconjunctivitis, being often characterized by the presence of both nasal and ocular symptoms) and chronic urticaria are common worldwide, with a prevalence ranging from 10% to 40% and from 0.6 to 2.6%, respectively.[1–3] Given the role of histamine in the pathogenesis of both conditions,

H_1-antihistamines represent the mainstay of treatment in both adults and children.[3,4]

Treatments for allergic rhinitis should be based on fast-acting, effective and non-sedating drugs.[5] According to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, an ideal oral H_1-antihistamine should possess the following characteristics: potency and selectivity in blocking H_1-receptors, quick onset and prolonged action, efficacy at relieving symptoms, lack of interaction with cytochrome P450 (CYP 450), absence of sedation or negative impact on cognitive or psychomotor functions, no anticholinergic activity, no association with cardiac adverse events and no potential for tachyphylaxis.[6] Most modern second-generation oral H_1-antihistamines meet these criteria:[7] due to their high selectivity for H_1-receptors, efficacy and minimal side-effects, they represent the H_1-antihistamines of choice for the treatment of allergic rhinitis in both adults and children.[8]

Amongst second-generation H_1-antihistamines, bilastine meets the highest number of the European Academy of Allergy & Clinical Immunology (EAACI)/ARIA criteria for the treatment of allergic rhinitis.[7,9–11] Several clinical trials in adults and adolescents have demonstrated the efficacy of bilastine 20 mg once daily for the treatment of seasonal allergic rhinitis or perennial allergic rhinitis (PAR);[5] in particular, in patients with allergic rhinoconjunctivitis, bilastine provided effective control of nasal obstruction and ocular symptoms.[12,13] Bilastine proved to be as effective as other oral second-generation H_1-antihistamines at reducing symptoms of allergic rhinitis (desloratadine, cetirizine and fexofenadine) and at improving health-related quality of life (QoL) (loratadine or desloratadine).[14–16] The incidence of adverse events recorded with bilastine in trials in allergic rhinitis was generally similar to that seen with placebo[14,17–19] and a lower frequency of somnolence and fatigue was observed with bilastine than with cetirizine:[17] this is important in the treatment of allergic rhinitis, which itself can cause somnolence and daytime sleepiness and impair psychomotor functions.[20–23]

The characteristics of the ideal antihistamine for the treatment of patients with acute and chronic urticaria should include the ability to relieve symptoms, rapid onset, long duration of action, once-daily administration and lack of side-effects such as drowsiness.[2] In children, it is important that urticaria treatment does not interfere with everyday life and school performance; therefore, first-generation antihistamines are not recommended, whereas a non-sedating antihistamine should be preferred.[24] Second-generation H_1-antihistamines show many of the characteristics of the ideal treatment for patients with urticaria, allowing long-lasting control of symptoms and warranting the well-being of the patient.[2]

After 1 day of treatment, bilastine induced significant improvements in patients with chronic spontaneous urticaria,[25,26] with rapid relief of wheal, flare and itching.[25–27] In adult patients with urticaria, bilastine showed a tolerability profile similar to placebo[25,26] and a safety profile entirely free from cardiovascular effects and not impairing psychomotor performance or driving ability.[28–31] In clinical studies, bilastine was shown to be non-sedating at therapeutic doses; furthermore, it did not potentiate the performance impairment associated with alcohol consumption or with treatment with the benzodiazepine lorazepam.[32,33] Bilastine 20 mg once daily was shown to improve QoL in patients with chronic spontaneous urticaria.[16,25,26]

The aim of our study was to outline the place of bilastine amongst current therapeutic options for allergic rhinitis and urticaria in adults and children. The results of the study were partially reported in a previous publication, focusing on the burden of allergic rhinoconjunctivitis and urticaria and the characteristics of bilastine compared with other therapeutic options.[34] Here, we report the results related to the specific role of bilastine in the treatment of each condition in both adults and children.

Methods

A modified Delphi process was performed to reach the abovementioned aim.[35,36]

The design and supervision of the study were assigned to a Scientific Committee, including eight key opinion leaders in the field of allergy (allergology, otorhinolaryngology, paediatric pulmonology, paediatric allergology and dermatology).

An Expert Panel, including 50 physicians from 17 countries (European and international) with documented experience in the field of allergic rhinitis and chronic urticaria, participated in the online voting.

The Scientific Committee elaborated a total of 27 statements, divided into three main topics: (1) burden of allergic rhinoconjunctivitis and urticaria and their impact on QoL; (2) current treatment options of rhinoconjunctivitis and urticaria and unmet needs; and (3) specific characteristics of bilastine amongst second-generation antihistamines.

The statements were voted by the Expert Panel through a dedicated web platform, using a five-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = undecided; 4 = agree; 5 = strongly agree). Consensus was defined as 80% concordance for 4+5 scores (agree or strongly agree).[37]

A previous publication reported the results of a selection of 15 statements related to (1) allergic diseases and their detrimental effect on QoL, sleep and daily activities, including job and school performance (statements 1–3); (2) current treatment options (including first-generation and second-generation H_1-antihistamines) and unmet needs (statements 4–8); and (3) characteristics of bilastine (statements 13a, 13b, 14, 21, 22, 23 and 24).[34]

The present publication focuses on results of the remaining 12 statements, related to (1) the ideal treatment of allergic rhinitis and urticaria in children and adults (statements 9–12); (2) bilastine for the treatment of allergic rhinitis (including efficacy, safety profile and effect on QoL; statements 15–17); and (3) bilastine for the treatment of urticaria (including efficacy, safety profile and effect on QoL; statements 18–20).

Results and discussion

By applying the predefined criteria for the definition of consensus (at least 80% agreement for 4+5 scores), all the 27 proposed statements reached consensus after the first round of voting. Amongst the 12 selected statements that are the focus of this publication, five statements reached a concordance of ≥98% and seven statements reached a concordance of ≥96% (Table 1).

The high degree of agreement obtained confirms a wide consensus on all covered issues. This is a valuable result, considering the varied composition of the Expert Panel, providing different points of view, and the method adopted (Delphi process), warranting anonymous responses.

The ideal treatment of allergic rhinitis in adults and children

Statement 9: *Patients with allergic rhinitis require a fast-acting, effective, and non-sedating treatment and most modern second-generation oral H_1-antihistamine agents meet these criteria.* (49 respondents, 96% agreement, 59% strongly agree)

The high degree of consensus reached for this statement suggests a shared awareness amongst clinicians about the needs of patients with allergic rhinitis and the goals of treatment. First-generation H_1-antihistamines, such as chlorphenamine and hydroxyzine, which are relatively non-specific and lipophilic, are more likely to lead to central nervous system effects and should not be recommended,[8] whereas second-generation compounds have negligible sedative effects and are recommended as first-line therapeutic options.[4,8]

Statement 10: *Second-generation H_1-antihistamines are the H_1-antihistamines of choice for treatment of allergic rhinitis in children due to their high selectivity for H_1-receptors, clinical efficacy, minimal adverse effects on cognition and long-term tolerability.* (49 respondents, 98% agreement, 71% strongly agree)

The sedative effect of first-generation H_1-antihistamines has occasionally been reported as 'desirable'; nevertheless, it can disrupt sleep patterns due to the impact in rapid eye movement (REM) phase of sleep and affect learning.[8] It is clear that a medication should not be prescribed for its side-effects, the extent of which is often unpredictable. Second-generation (non-sedating) H_1-antihistamines are preferred because they are well tolerated over a long period and have fewer adverse effects on cognition.[8]

The ideal treatment of urticaria in adults and children

Statement 11a (acute urticaria): *The ideal antihistamine for the treatment of acute urticaria should be effective in relieving symptoms, have a rapid onset of action and not cause unwanted effects such as drowsiness.* (49 respondents, 98% agreement, 86% strongly agree)

Statement 11b (chronic urticaria): *The ideal antihistamine for the treatment of chronic urticaria should be effective in relieving symptoms, have a long duration of action, preferably be administrated once daily and not cause unwanted effects such as drowsiness.* (49 respondents, 96% agreement, 88% strongly agree)

Statement 11c (recommended first-line treatment): *Second-generation H_1-antihistamines fit the profile of the ideal antihistamine for the treatment of acute and chronic urticaria and are therefore recommended as first-line therapy.* (49 respondents, 96% agreement, 76% strongly agree)

The agreement recorded on the ideal profile of the antihistamine for treatment of urticaria is in line with the position of the EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline on urticaria, which recommends second-generation H_1-antihistamines at licensed doses as first-line therapy for patients with urticaria[2] based on their ability to stabilize the histamine H_1-receptor in their inactive state.[38] As chronic pharmacological treatment is required to control symptoms, it is important to choose drugs with a positive tolerability profile.[24] In this respect, the use of sedating antihistamines, which are associated with potential serious side-effects, is not recommended for the routine management of chronic urticaria.[39] Based on their good safety profile, second-generation antihistamines should be considered as the first-line symptomatic treatment for urticaria.[2]

Statement 12: *Urticaria treatment itself should not interfere with everyday life and school performance.*

Table 1. Results obtained from the Delphi process for the selected statements.

Statement	Results		
Treatment	**Number of respondents**	**Percentage agreement (scores 4+5)**	**Median score (IQR)**
9. Patients with allergic rhinitis require a fast-acting, effective, and non-sedating treatment and most modern second-generation oral H_1-antihistamine agents meet these criteria.	49	96	5 (1)
10. Second-generation H_1-antihistamines are the H_1-antihistamines of choice for treatment of allergic rhinitis in children due to their high selectivity for H_1-receptors, clinical efficacy, minimal adverse effects on cognition and long-term tolerability.	49	98	5 (1)
11a. The ideal antihistamine for the treatment of acute urticaria should be effective in relieving symptoms, have a rapid onset of action and not cause unwanted effect such as drowsiness.	49	98	5 (0)
11b. The ideal antihistamine for the treatment of chronic urticaria should be effective in relieving symptoms, have a long duration of action, preferably be administrated once daily and not cause unwanted effect such as drowsiness.	49	96	5 (0)
11c. Second-generation H_1-antihistamines fit the profile of the ideal antihistamine for the treatment of acute and chronic urticaria and are therefore recommended as first-line therapy.	49	96	5 (1)
12. Urticaria treatment itself should not interfere with everyday life and school performance. Therefore, the recommended first-line treatment for urticaria in children is with second-generation non-sedating antihistamines.	49	98	5 (0)
Bilastine			
15. Owing its pharmacological profile, bilastine meets most of the EAACI/ARIA criteria for medications used in the treatment of allergic rhinitis.	48	96	5 (1)
16. The overall incidence of adverse events with bilastine in trials in allergic rhinitis was generally similar to that seen with placebo. The low incidence of somnolence of bilastine could be of great value as allergic rhinitis itself can have a sedative effect and impair psychomotor functions in affected patients.	48	96	5 (1)
17. Bilastine was demonstrated to be effective in improving health-related QoL in patients with allergic rhinitis, contrasting the marked negative impact of the disease on many areas of daily activity.	48	96	5 (1)
18. Patients with urticaria could benefit from bilastine administration due to its results in effective reduction of chronic spontaneous urticaria symptoms, itching sensation included.	48	98	5 (1)
19. Bilastine is well tolerated in adult patients with urticaria, with an overall incidence of adverse events similar to that seen with placebo, which remains unchanged in the long term, with no evidence of increased sedation over time or interference with driving ability or psychomotor functions.	48	96	5 (1)
20. Bilastine improves QoL in patients with chronic spontaneous urticaria, contrasting the considerable adverse effect of the disease on patients' daily activities, even in the long term.	48	98	5 (1)

Therefore, the recommended first-line treatment for urticaria in children is with second-generation non-sedating antihistamines. (49 respondents, 98% agreement, 78% strongly agree)

Sedating H_1-antihistamines are often used as first choice in the treatment of children with allergies, especially by general practitioners and paediatricians,[40] probably because of a longer experience with them.[38] However, a strong recommendation was made to discourage the use of first-generation antihistamines in infants and children. In the paediatric population, only medications whose long-term safety has been well established (such as cetirizine, desloratadine, fexofenadine, levocetirizine,

rupatadine, bilastine and loratadine)[38] are recommended as first-line therapy for the management of chronic spontaneous urticaria.[8]

Bilastine for the treatment of allergic rhinitis

Statement 15: *Owing its pharmacological profile, bilastine meets most of the EAACI/ARIA criteria for medications used in the treatment of allergic rhinitis.* (48 respondents, 96% agreement, 71% strongly agree)

The observed consensus demonstrates the widespread knowledge of existing evidence amongst experts. In European individuals, bilastine 20 mg showed a rapid onset of action, similar to cetirizine 10 mg, and a longer duration of action compared with fexofenadine 120 mg;[41] in Japanese individuals, the onset of action of bilastine 20 mg was faster than that of fexofenadine 60 mg.[42] The efficacy of bilastine 20 mg once daily in adults/adolescents with seasonal allergic rhinitis or PAR was higher than placebo and similar to desloratadine 5 mg once daily, cetirizine 10 mg once daily or fexofenadine 60 mg twice daily in terms of symptom reduction.[14,17–19] In patients with PAR, the reductions in Total Symptom Score, Total Nasal Symptom Score and Total Ocular Symptoms Score as well as the improvement in QoL obtained with bilastine 20 mg once daily were maintained for up to 1 year.[43]

Statement 16: *The overall incidence of adverse events with bilastine in trials in allergic rhinitis was generally similar to that seen with placebo. The low incidence of somnolence of bilastine could be of great value as allergic rhinitis itself can have a sedative effect and impair psychomotor functions in affected patients.* (48 respondents, 96% agreement, 56% strongly agree)

Allergic rhinitis can cause sedation and impair psychomotor functions, with a negative impact on driving ability[20,22] or academic performance;[44] therefore, it is advisable that antihistamine treatment does not interfere with vigilance and cognitive functions.[20,22] The occurrence of adverse events was less frequent with bilastine 20 mg once daily than with cetirizine 10 mg once daily, both for somnolence (1.8 *versus* 7.5%; $p<0.001$) and fatigue (0.4 *versus* 4.8%; $p=0.02$).[17] Treatment of patients with allergic rhinitis with bilastine for up to 1 year was shown to be safe and well tolerated.[43]

Statement 17: *Bilastine was demonstrated to be effective in improving health-related QoL in patients with allergic rhinitis, contrasting the marked negative impact of the disease on many areas of daily activity.* (48 respondents, 96% agreement, 54% strongly agree)

Allergic rhinitis causes limitations in daily activities, reducing concentration, productivity, sleep and sexual function,[45,46] with a negative impact on QoL and a substantial economic burden on the healthcare system.[47] The improvement of health-related QoL induced by bilastine 20 mg once daily in patients with allergic rhinitis was similar to that observed with loratadine 10 mg or desloratadine 5 mg once daily.[14–16]

Bilastine for the treatment of urticaria

Statement 18: *Patients with urticaria could benefit from bilastine administration due to its results in effective reduction of chronic spontaneous urticaria symptoms, itching sensation included.* (48 respondents, 98% agreement, 67% strongly agree)

The high degree of consensus recorded for the benefits of bilastine in the treatment of urticarial symptoms is supported by available evidence. Bilastine 20 mg once daily was significantly more effective than placebo[25,26] and as effective as levocetirizine 5 mg once daily at reducing the symptoms of chronic spontaneous urticaria (assessed using Total Symptom Score).[25] Bilastine was also significantly better than desloratadine and rupatadine for reducing itching sensation in healthy volunteers injected with intradermal histamine to induce a wheal and flare response, whereas neither desloratadine nor rupatadine significantly reduced itching compared with placebo.[48] In patients with moderate-to-severe chronic spontaneous urticaria not responding to other H_1-antihistamines at licensed doses, switching to bilastine 20 mg once daily for 2 weeks produced a mean decrease of Urticaria Activity Score over seven consecutive days of 37% and a decrease of 44% and 29% of the pruritus and wheal components, respectively.[49]

Statement 19: *Bilastine is well tolerated in adult patients with urticaria, with an overall incidence of adverse events similar to that seen with placebo, which remains unchanged in the long term, with no evidence of increased sedation over time or interference with driving ability or psychomotor functions.* (48 respondents, 96% agreement, 65% strongly agree)

These results demonstrate a complete awareness by the Expert Panel of the safety profile of bilastine, in line with available evidence. In adult patients with chronic spontaneous urticaria or pruritus treated for 1 year, bilastine was well tolerated, showing no significant effect on QTc interval.[50–53] The occurrence of somnolence and fatigue was significantly less frequent with bilastine than with cetirizine.[5] Bilastine at the therapeutic dose of 20 mg for 1 week exerted no negative effects on attention and reactivity levels in patients with allergies performing a Formula 1-high speed simulator driving test.[54]

Statement 20: *Bilastine improves QoL in patients with chronic spontaneous urticaria, contrasting the*

considerable adverse effect of the disease on patients' daily activities, even in the long term. (48 respondents, 98% agreement, 56% strongly agree)

QoL is impaired in patients with chronic urticaria.[55,56] Improvements in QoL were observed in patients with chronic spontaneous urticaria treated with bilastine 20 mg once daily[16,25,26] as suggested by the significant decrease of the mean Dermatology Life Quality Index (DLQI) global score observed with bilastine *versus* placebo after 4 weeks in a large, randomized trial (−9.45 *versus* −5.93; $p<0.001$).[25]

Study limitations

The results of the present study, though of potential clinical relevance, were obtained through a modified Delphi method, a procedure often used to evaluate consensus amongst experts on issues of particular interest: the main limitation of such studies is that their results mainly reflect the current knowledge and clinical expertise of the involved clinicians rather than adding new evidence. However, as the proposed statements were elaborated based on the existing scientific literature, the reported results reflect the evidence-based position of experts in the field of allergic rhinitis and urticaria on the current treatment options of these conditions, which may be useful to clinicians in their everyday clinical practice. Another limitation of our study may be the performance of a single round of voting; however, given the high degree of consensus obtained after the first round, the contribution of further voting rounds was expected to be irrelevant.

Conclusions

The reported results confirm the recognized role of second-generation H_1-antihistamines in the management of both allergic rhinitis and urticaria, highlighting the potential advantages of bilastine in terms of both symptom control and tolerability.

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