Review Article

Expert opinion on the role of bilastine and bilastine-montelukast combination in the management of allergic rhinitis: An Indian perspective

Subir Jain[1], Sarika Verma[2], Santhalingam Balamurugan[3], K.R. Bharath Kumar Reddy[4], D.J. Christopher[5]

[1]Senior Consultant ENT Surgeon and Allergologist, Dr Subir Jain's ENT Centre, Indore, MP, India, [2]Senior ENT Surgeon and Allergy Specialist, Director, AllergyDoc Clinics, Gurgaon, Haryana, India, [3]Professor, Department of Pulmonary Medicine, A.C.S. Medical College and Hospital, Chennai, and Principal Investigator & Director – Respiratory Clinical Trials at Chest Research Institute, Chennai, Tamil Nadu, India, [4]Paediatric Pulmonologist, Director, Shishuka Children's Hospital, Bengaluru, Karnataka, India, [5]Professor, Department of Pulmonary Medicine, The Christian Medical College & Hospital, Vellore, Tamil Nadu, India; Vice-President (and Co-Founder) of the Indian Association of Respiratory Care; Chair, Research committee & Past President, Indian Chest Society.

Abstract

In India, the burden of allergic rhinitis (AR) is enormous, comprising 55% of all patients with allergies. Intranasal corticosteroids are the recommended first-line therapy for patients with moderate-to-severe AR, particularly when nasal congestion is the predominant symptom. However, second-generation antihistamines are the first line of treatment in mild AR and effectively improve symptoms, such as sneezing, itching, and rhinorrhoea. Bilastine is a second-generation H_1-antihistamine indicated for the symptomatic treatment of allergic rhinoconjunctivitis in adults and adolescents over 12 years of age. Though it is an effective individual molecule for the management of AR, studies have shown that synergistic combination therapy of bilastine-montelukast has a dual action on early- and late-phase allergic reactions in AR patients with concomitant asthma. An advisory board meeting was conducted (on a virtual platform) to gain insights from Indian experts on the following: (i) burden of AR and AR with concomitant asthma in Indian settings; (ii) current unmet needs; and (iii) role and positioning of bilastine and bilastine plus montelukast combination in the management of AR and AR with concomitant asthma in adults and adolescents over 12 years of age. The experts shared their opinions based on the *available scientific evidence* and/or *clinical expertise or experience*. In this article, we have summarized the highlights of the expert panel discussion and available evidence for each of these topics.

Keywords: *allergic rhinitis, antihistamine, asthma, expert opinion, guidelines, India, management*

***Key Message**: Bilastine is a second-generation H_1-antihistamine indicated for the symptomatic treatment of allergic rhinoconjunctivitis in adults and adolescents over 12 years of age. Montelukast, a highly selective cysteinyl leukotriene type-1 (CysLTR1) antagonist, is used to control and prevent symptoms of asthma and allergic rhinitis. The synergistic combination of bilastine plus montelukast has a dual action and is an attractive treatment option in allergic rhinitis patients with hyperreactive airway disease such as asthma. Both classes of drugs are required for achieving better results.*

Received: 23 December 2022
Accepted: 18 February 2023
Published: 25 April 2023

Introduction

Allergic respiratory diseases have become a major health distress globally, with India being no exception.[1] Allergic diseases, such as bronchial asthma, atopic rhinitis, dermatitis, urticaria, ocular allergy and life-threatening anaphylaxis, affect a

Access this article online

Quick Response Code:

Website: www.jacpjournal.org

DOI: 10.4103/jacp.jacp_45_22

Address for correspondence: D J Christopher, Professor, Department of Pulmonary Medicine, The Christian Medical College & Hospital, Vellore, Tamil Nadu; Vice-President (and Co-Founder) of the Indian Association of Respiratory Care; Chair, Research committee & Past President, Indian Chest Society.
E-mail: djchris@cmcvellore.ac.in

How to cite this article: Jain S, Verma S, Balamurugan S, Reddy KK, Christopher D. Expert opinion on the role of bilastine and bilastine-montelukast combination in the management of allergic rhinitis: An Indian perspective. J Assoc Chest Physicians 2023;11:1-9.

substantial population of all ages in different parts of India.[1] According to the World Allergy Organization, the global prevalence of allergy ranges between 10% and 40% across all age groups.[2] In India, the burden of allergic rhinitis (AR) is enormous, comprising 55% of all patients with allergies.[3] The reported incidence of AR in India ranges between 20% and 30%.[3] Current management options for AR include allergen avoidance, use of immunotherapy, and antiallergic medications for symptomatic relief.[4,5] Intranasal glucocorticosteroids are recommended as first-line therapy for patients with moderate-to-severe AR, particularly when nasal congestion is the predominant symptom.[6] Second-generation H_1-antihistamines are the first line of treatment in mild-to-moderate AR and effectively improve symptoms, such as sneezing, itching, and rhinorrhoea.[6-8] Bilastine, a second-generation H_1-antihistamine, is indicated for the symptomatic treatment of allergic rhinoconjunctivitis (ARC) characterized by rhinorrhoea, sneezing, and nasal itch in adults and adolescents over 12 years of age.[8,9] Montelukast is a leukotriene receptor antagonist (LTRA) with similar benefits as antihistamines when used as monotherapy for the treatment of seasonal AR (SAR).[10] The drug has a high affinity for the cysteinyl leukotriene type-1 ($CysLT_1$) receptor and a targeted dual mechanism of action (bronchodilator and anti-inflammatory effects) to control and prevent symptoms caused by asthma (such as wheezing and shortness of breath) and AR.[11] The synergistic combination of bilastine-montelukast therapy can have a dual action on early- and late-phase allergic reactions in AR patients. Both drugs in combination can be used in the treatment of AR and mild-to-moderate asthma. In this article, we have reviewed the burden of AR and AR with concomitant asthma in India. We have gathered and summarized key information on the role and positioning of bilastine and bilastine plus montelukast combination in the management of AR and AR with concomitant asthma in adults and children, based on the expert panel discussion.

Methodology

An advisory board meeting was convened on 8 June 2021, on a virtual platform, to gain insights from experts on AR and its management. The members of the advisory board were selected to best represent the breadth of knowledge and clinical experience in the field of allergy and immunology from all over India. The key purpose of the meeting was to (i) understand the burden of AR and AR with concomitant asthma in Indian settings; (ii) discuss guideline recommendations and current unmet needs; and (iii) gain insights into the role and positioning of bilastine and bilastine plus montelukast combination in the management of AR and AR with concomitant asthma in adults and adolescents over 12 years of age. A literature review was carried out based on data from the PubMed Database to identify relevant articles between January 2001 and June 2021 using keywords, such as "India," "adults," "children," "burden," "allergic rhinitis," "asthma," "bilastine," "antihistamines," "montelukast," "antihistamine," "guidelines," and "management." During the advisory board meeting, in addition to the interactive discussion, a qualitative question-and-answer based format was used to facilitate discussion. After the group discussion, key expert opinions were formulated based on the opinions and agreement of the majority. Highlights of the discussion were emailed to the experts present during the advisory board for a final review.

Results and Discussion

Epidemiology and Burden of AR and AR with Concomitant Asthma in Indian Settings

In India, the burden of AR is enormous, comprising 55% of all patients with allergies.[3] The reported incidence of AR in India ranges between 20% and 30%.[3] In India, the International Study of Asthma and Allergies in Childhood (ISAAC) Phase I revealed that 12.5% of children in the age group of 6 to 7 years and 18.6% in the age group of 13 to 14 years had nasal symptoms alone, whereas ARC was seen in 3.3% and 5.6% of children in these age groups, respectively.[12] However, in ISAAC Phase III, the prevalence of nasal symptoms increased to 12.9% and 23.6% in the age groups of 6 to 7 years and 13 to 14 years, respectively, whereas the prevalence of ARC increased to 3.9% and 10.4%, respectively.[12]

Clinical Profile of Patients with AR in India: The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend the classification of AR patients [Figure 1] based on the duration of symptoms (intermittent or persistent) and the severity of the disease (mild, moderate, or severe).[6,13] AR is further classified as sneeze runners and blockers based on the clinical profile of the patient. In sneeze runners, the main symptoms are sneezing, rhinorrhoea, and itchy nose and eyes.[3] In contrast, blockers have nasal congestion as the prime symptom, wherein nasal blockage and thick mucus can lead to postnasal drip and breathlessness.[3] Nasal obstruction, runny nose, sneezing, and itching are the common symptoms seen in Indian adults with AR.[3] The presence of AR is studied as a risk factor for both the incidence and severity of asthma.[14,15]

A study published by Jaggi V *et al.* studied the prevalence of AR with concomitant asthma by conducting a nationwide epidemiological survey across 10 cities in India (Delhi, Lucknow, Meerut, Kolkata, Jaipur, Mumbai, Chennai, Hyderabad, Thiruvananthapuram, Bengaluru).[15] The study found that the prevalence of

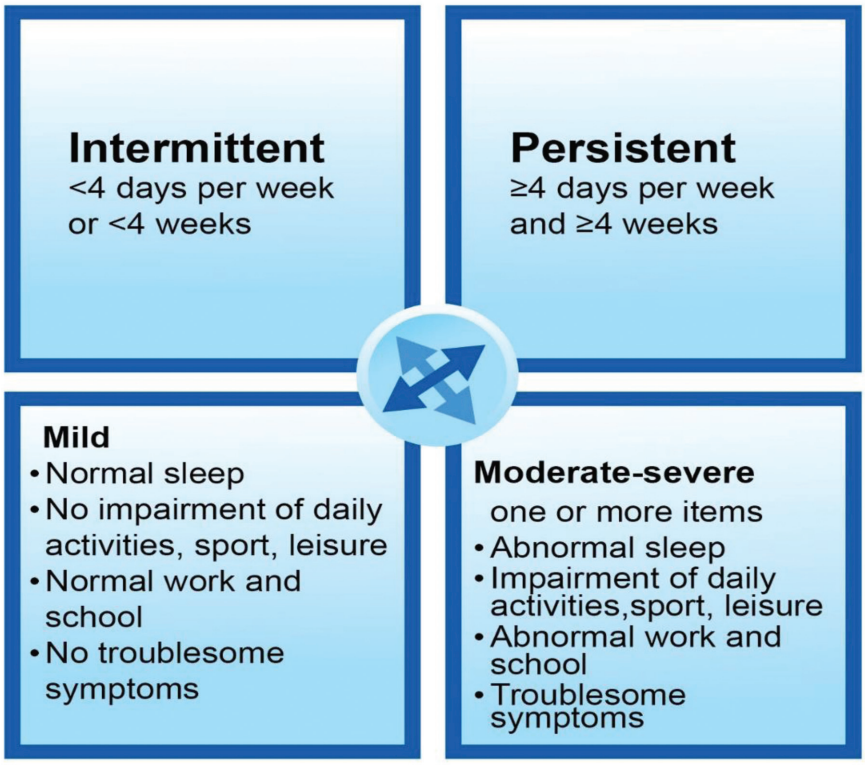

Figure 1: Classification of AR according to symptom duration and severity. Adapted from: Bro ek JL et al. 2017[13] and Varshney J et al. 2015[6]. AR: allergic rhinitis.

AR with concomitant asthma was 65.24%, and nearly 17% of patients had never been diagnosed with AR beforehand.[15] The presence of asthma-AR coexistence was found to be the highest in the age group of 19 to 44 years; the prevalence was found to decrease with increasing age (>65 years).[15]

Guideline Recommendations for the Management of AR and AR with Concomitant Asthma

Intranasal glucocorticosteroids (INCS) are the recommended first-line therapy for patients with moderate-to-severe AR, particularly when nasal congestion is the predominant symptom.[6] Antihistamines are the first line of treatment in mild AR and effectively improve symptoms, such as sneezing, itching, and rhinorrhoea.[7] However, antihistamines have only a modest effect on nasal congestion compared with INCS.[6] [Figure 2] depicts the ARIA guidelines for AR management.[4] The American Academy of Otolaryngology – Head and Neck Surgery guidelines recommend second-generation/less-sedating oral H_1-antihistamines for patients with AR and primary complaints of sneezing and itching.[13] The ARIA guidelines suggest that the choice of the LTRA or oral H_1-antihistamines would mostly depend on patient preferences for the affected outcomes, local availability, and the cost of specific medications.[13] The guidelines suggest that patients with AR who have concomitant asthma, especially exercise-induced and/or aspirin-exacerbated respiratory disease, might benefit from an LTRA more than from an oral H_1-antihistamine.[13] However, this recommendation applies to the treatment of AR but not to the treatment of asthma. [Table 1] provides a list of pharmacotherapy options for treating AR. The American Academy of Family Physicians makes no specific recommendation for the use of LTRAs versus oral H_1-antihistamines but suggests that montelukast, though less effective than INCS, is comparable with oral H_1-antihistamines and may be particularly useful in patients with coexistent asthma.[13]

Role and Positioning of Bilastine in the Management of AR

Bilastine is a novel second-generation H_1-antihistamine approved for the symptomatic treatment of ARC (seasonal and perennial) and urticaria in adults and children over 12 years of age.[8] [Table 2] provides a comparison of the clinical profile between bilastine and various second-generation H_1-antihistamines.[16] Bilastine has high H_1-receptor selectivity and negligible affinity for other receptors, and demonstrates antiallergic properties.[16-18] Bilastine has a rapid onset of action and has been shown to have a long residence time at the H_1 receptor, ensuing prolonged receptor antagonism, with 60% to 70% antagonism marked 24 hours after dosing.[18] It is rapidly absorbed after oral administration (oral

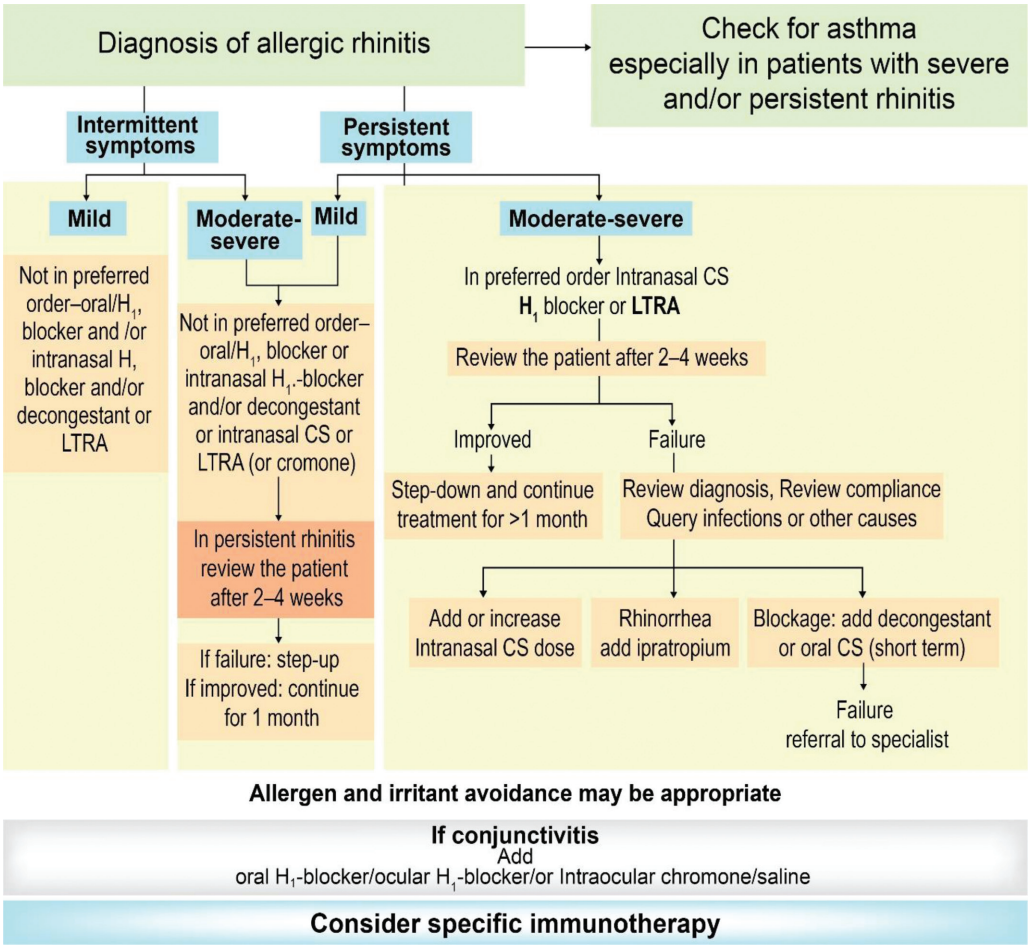

Figure 2: Management of AR as per ARIA recommendations Adapted from: Bousquet J et al., 2008[4]. AR: allergic rhinitis; ARIA: Allergic Rhinitis and its Impact on Asthma; LRTA: leukotriene receptor antagonist; CS: corticosteroid.

bioavailability: 60%), achieving maximum plasma concentrations after 1 to 1.5 hours.[18] Bilastine does not undergo significant hepatic metabolism and approximately 95% of the drug is excreted unchanged in the faeces (67%) or urine (33%).[18] The recommended dose of bilastine is 20 mg once daily (OD) in adults and adolescents (12 years of age and above) and best taken at least 1 hour before or 2 hours after the intake of food or fruit juice.[19] Bilastine is a nonsedating, non-brain-penetrating antihistamine and does not affect psychomotor or driving performance even at twice the recommended dose of 20 mg.[20] Compared with other second-generation antihistamines, bilastine (20 mg OD) does not exhibit anticholinergic effects or cardiotoxic effects and no dosage adjustments are required in patients with renal or hepatic impairment or elderly patients.[16,17]

A study published by Horak F *et al.* compared the potential of bilastine 20 mg and fexofenadine 120 mg to relieve the symptoms of AR in adult patients ($N = 75$, aged 18–55 years).[21] Bilastine 20 mg, fexofenadine 120 mg, or placebo was taken orally 2 hours after the start of provocation on Day 1 of the study. The study assessed the following: (i) total nasal symptom scores (TNSS) composed of the sum of four individual symptom scores (sneezing, rhinorrhoea, nasal obstruction, and nasal itching); (ii) global symptom scores assessed as the composite score (nasal obstruction, rhinorrhoea, itchy nose, sneezing, watery eyes, itchy eyes, cough, itchy throat, itchy ears); (iii) nasal secretions; and (iv) eye symptoms on both Day 1 and Day 2.[21] The study concluded that bilastine 20 mg was significantly more effective in reducing TNSS, global symptom score, nasal secretions, and eye symptoms 22 to 26 hours after drug administration than fexofenadine.[21] Another study published by Kuna P *et al.* compared the efficacy and safety of bilastine 20 mg OD for 2 weeks with cetirizine 10 mg or placebo OD in SAR patients ($N = 683$ patients, aged 12–70 years) at the height of the pollen season.[22] The primary efficacy measure was the area under the curve (AUC) of reflective total symptom scores (TSS) over 2 weeks of treatment (TSS-$AUC_{0–14\ days}$).[22] The secondary efficacy measures included mean change from baseline in

Table 1: Pharmacotherapy Options for the Management of AR

Pharmacotherapy Options for Treating AR	Generic Name	Mechanism of Action	Side Effects	Comments
Oral H_1-antihistamines	**Second generation** • Acrivastine • Cetirizine • Bilastine • Fexofenadine • Levocetirizine • Mequitazine **First generation** • Chlorpheniramine • Clemastine • Hydroxyzine	Relieve symptoms of AR by blockage of H_1 receptor	• Acrivastine has sedative effects • Mequitazine has an anticholinergic effect. • In old-generation oral antihistamines,sedation and anticholinergic effects are common	○ New-generation oral H_1-antihistamines should be preferred for their favorable efficacy/safety ratio and pharmacokinetics ○ Rapidly effective (<1 hour) on nasal and ocular symptoms ○ Moderately effective on nasal congestion
Local H_1-antihistamines (intranasal, intraocular)	• Azelastine • Levocabastine	Relieve symptoms of AR by blockage of H_1 receptor	• Minor local side effects. Azelastine: bitter taste	Rapidly effective (<30 minutes) on nasal or ocular symptoms
INCS	• Fluticasone furoate • Mometasone furoate • Beclomethasone dipropionate	• Potently reduce nasal inflammation • Reduce nasal hyper-reactivity	• Minor local side effects • Wide margin for systemic side effects	○ Effective on nasal congestion ○ Effect observed after 12 hours but maximal effect after a few days of therapy
LTRAs	• Montelukast • Pranlukast • Zafirlukast	Inhibit the effect of leukotrienes. Block $CystLT_1$ receptor	Excellent tolerance	○ Effective on rhinitis and asthma ○ Effective on all symptoms of rhinitis and ocular symptoms
Oral decongestants	• Ephedrine • Phenylephrine • Phenyl propanolamine • Pseudoephedrine	Sympatho-mimetic drugs cause vasoconstriction and provide relief from the symptoms of nasal congestion in AR patients	Hypertension, palpitations, insomnia, headache, dry mucous membranes, urinary retention, exacerbation of glaucoma or thyrotoxicosis	Use oral decongestants with caution in patients with heart disease
Intranasal decongestants	• Oxymetazoline • Xylometazoline	Sympatho-mimetic drugs cause vasoconstriction and provide relief from the symptoms of nasal congestion in AR patients	Same side effects as oral decongestants but less intense	Act more rapidly and more effectively than oral decongestants **Note:** Limit duration of treatment to <10 days to avoid rhinitis medicamentosa
Oral/IM gluco-corticosteroids	• Dexamethasone • Hydrocortisone • Methylprednisolone • Prednisolone • Prednisone • Triamcinolone	Potently reduce nasal inflammation andreduce nasal hyperreactivity	○ Systemic side effects common, in particular for IM drugs ○ Depot injections may cause local tissue atrophy	○ When possible, INCS should replace oral or IM drugs. However, a short course of oral glucocorticosteroids may be needed in case of moderate/severe symptoms.

Adapted from: Bousquet J et al., 2008[4] and Dykewicz MS et al., 2017[5]. AR: allergic rhinitis; $CysLT_1$: Cysteinyl leukotriene type-1; INCS: intranasal glucocorticosteroids; IM: intramuscular; LTRA: leukotriene receptor antagonists

Table 2: Clinical Profile Differences between Various Second-Generation H_1-Antihistamines

Characteristic	Bilastine	Cetirizine	Ebastine	Fexofenadine	Levocetirizine	Loratadine
H_1-receptor selectivity	+++	+	++	+	++	+
t_{max} (hours)	1.3	1.0	2.6–4.0 (carebastine metabolite)	1–3	0.9	1.0–1.5
Indicated for allergic rhinoconjunctivitis	Yes	Some but not all formulations	No	No	No	No
Indicated for AR	Yes	Yes	Yes	Yes	Yes	Yes
Paediatric indication	No	Children aged 6–12 years	Children aged ≥2 years	Children aged ≥3 years	Children aged ≥2 years	Children aged ≥2 years
Dosage adjustment in renal impairment	No	Yes (when moderate-to-severe)	Caution	No	Yes (when moderate-to-severe)	No
Dosage adjustment in hepatic impairment	No	Yes (if with concomitant renal dysfunction)	Caution (when mild-to-moderate)	No	Yes (if with concomitant renal dysfunction)	Yes (severe disease)
Dosage adjustment in the elderly	No	No (if renal function is correct)	No	No	Yes (for concomitant moderate-to-severe renal impairment)	No
Contraindications	No	Severe renal impairment	Severe hepatic impairment	No	Severe renal impairment	No
Number of ARIA-recommended antihistamine properties	10	6	6.5	9.5	6.5	6.5

Adapted from: Wang XY et al., *2016*[16]. +: Mild; ++: Moderate; +++: Marked. AR: allergic rhinitis; ARIA: Allergic Rhinitis and its Impact on Asthma; t_{max}: time to peak plasma concentration

the TSS, nasal symptom score (NSS), non-nasal symptom score (NNSS), and discomfort caused by AR. The mean TSS-$AUC_{0–14\ days}$ was significantly lower with bilastine (76.5) and cetirizine (72.3) treatment compared with placebo (100.6, $p < 0.001$).[22] Bilastine 20 mg and cetirizine 10 mg were significantly better than placebo with respect to changes in the NSS and NNSS throughout the study and by the end of treatment ($p < 0.001$).[22] However, significantly fewer patients in the bilastine-treated SAR group, compared with the cetirizine-treated group, experienced somnolence (1.8% versus 7.5%; $p < 0.001$) and fatigue (0.4% versus 4.8%; $p = 0.02$) during the study.[22] Another prospective, multicenter, observational study published by Sologuren A *et al.* evaluated the safety profile of bilastine 20 mg in elderly patients (aged ≥65 years) ARC and/or urticaria. The most frequent nonserious treatment-emergent adverse events (TEAEs) reported in the study were infections and infestations (15.8%), muscle and connective tissue injuries (9.6%), and gastrointestinal disorders (8.2%).[23] The study concluded that the incidence of TEAEs was low, with monthly and quarterly rates of 0.29 and 0.88, respectively. All serious TEAEs were considered to be unrelated to bilastine.[23] More recently, 10 mg of bilastine has been approved in Europe for use in children aged 6 to 11 years with a body weight of at least 20 kg.[9,17,18] Ocular symptoms often accompany AR and can cause inconvenience to the patient as much as or even more than the actual nasal symptoms.[24,25] Bilastine 20 mg was found to be significantly more effective at relieving ocular symptoms ($p < 0.001$), including both reflexive and instantaneous symptoms (itching, tearing, and conjunctival redness), than placebo.[24] Novák Z *et al.* assessed the efficacy and safety of 10 mg of bilastine OD in children aged 2 to 11 years with ARC or chronic urticaria for 12 weeks.[26] Bilastine was administered in two forms: (i) as a 10 mg oral dispersible tablet dissolved in water in children aged 2 to younger than 6 years; and (ii) tablet swallowed or dissolved in water in children aged 6 to younger than 12 years.[26] After 12 weeks of treatment, there was no statistically significant difference between the safety and tolerability profile of bilastine 10 mg OD versus placebo in children with ARC or chronic urticaria.[26]

Experts' Opinions: Role and Positioning of Bilastine in the Management of AR

(1) The experts strongly opined that bilastine 20 mg OD is a good drug for the management of AR symptoms in adults and adolescents (≥12 years of age). Bilastine should be taken orally 1 hour before food or 2 hours after the intake of food. The drug is well tolerated in the majority of AR patients, with minimal sedative effects in this category of AR patients.

Treatment-related side effects observed in some patients (<1%) were insomnia, acidity, and a burning sensation while urinating.

(2) More recently, bilastine has been approved widely for use in children aged 6 to 11 years. However, the experts suggested that more studies need to be conducted for evaluating the efficacy and long-term safety of bilastine in this subgroup of the patient population.

(3) The experts mentioned that currently, bilastine is not recommended for the treatment of AR in children less than 6 years of age.

Role and Positioning of Bilastine-Montelukast Combination in the Management of AR and AR with Concomitant Asthma

Liu G and colleagues compared the efficacy of oral H_1-antihistamines plus LTRAs versus H_1-antihistamines alone for the management of patients with AR.[27] The study found that combination therapy of LTRAs plus oral H_1-antihistamines can increase the therapeutic efficacy against daytime and composite nasal symptoms, including rhinorrhoea, sneezing, and itching.[27] Conversely, it does not affect night-time nasal symptoms and eye symptoms.[27] The study also suggested that the patients with perennial AR may benefit more from the combination therapy of LTRAs plus oral H_1-antihistamine.[27] Histamine and $CysLT_1$ are potent inflammatory mediators involved in both seasonal ARC and asthma.[28] Bilastine is a selective antagonist of peripheral H_1-receptors and montelukast is an LTRA with a high affinity for the $CysLT_1$ receptor.[28] Montelukast has been proven to be effective in exercise-induced asthma and asthma associated with AR.[29] Other phenotypes where montelukast therapy is effective include asthma in obese patients, asthma in smokers, aspirin-induced asthma, and viral-induced wheezing episodes.[29] The synergistic combination of bilastine-montelukast therapy has a dual action on early- and late-phase allergic reactions in AR patients.[28] Montelukast 10 mg is rapidly absorbed after oral administration (mean oral bioavailability of 64%), with a peak plasma concentration being reached within 3 to 4 hours in adults.[30] After absorption, montelukast is over 99% bound to plasma proteins and is extensively metabolized by cytochrome P450 isoenzymes 3A4 and 2C9.[30] Plasma clearance of montelukast is approximately 45 mL/minute in healthy adults and is excreted along with its metabolites via bile (elimination half-life is 4 to 5 hours).[30,31]

In children, INCS are currently considered as the gold-standard treatment for the long-term management of mild persistent asthma, with LTRA as a second-line alternative.[32,33] Montelukast is the only LTRA licenced for use in children <12 years of age and is generally well tolerated, with side effects primarily limited to minor gastrointestinal disturbances, respiratory symptoms, skin reactions, and headaches.[33] Studies have shown that when added to INCS, montelukast induced further improvement in pulmonary function and symptoms of asthma, particularly in patients poorly controlled on INCS alone.[29] However, recently, serious neuropsychiatric events, such as aggressive behavior, depression, hallucinations, and suicidal tendencies have been observed in some patients with the use of montelukast, which questions its long-term safety.[33] A study by Van Adelsberg *et al.* evaluated the efficacy and tolerability of montelukast 10 mg given OD in adolescents and adults ($N = 1,079$, aged 15–82 years) for seasonal AR.[34] The study concluded that montelukast was more effective in improving scores for daytime nasal symptoms ($p = 0.003$) and secondary endpoints of night-time, daytime eye symptoms, and quality of life ($p = 0.006$) compared with placebo.[34] Discontinuations due to AEs were infrequent and comparable between the montelukast and placebo groups.[34] Another study published by Virchow JC *et al.* studied the efficacy and safety of montelukast 10 mg in adults with AR and concomitant asthma.[35] Following treatment with 10 mg montelukast, around 86.5% of patients reported a strong or marked improvement in daytime asthma symptoms and 88.5% of patients reported improvement in night-time AR symptoms.[35] The use of montelukast therapy significantly ($p < 0.001$) reduced nasal congestion, rhinorrhoea, sneezing, and daytime eye symptoms, and improved the quality of life.[35] Montelukast was well tolerated with no serious AEs. The most frequently observed side effects during the study were headache, gastrointestinal infections, and sleepiness.[35] Lavorini F *et al.* assessed the efficacy and safety of concomitant therapy of bilastine and montelukast versus monotherapy (bilastine or montelukast) in patients with seasonal ARC and mild-to-moderate asthma.[28] Bilastine alone improved seasonal ARC symptoms more than montelukast in the first 2 weeks of treatment due to the rapid onset of action of bilastine compared with montelukast.[28] Mean TSS observed in the first and second weeks after bilastine was significantly ($p < 0.05$) lower than after montelukast therapy. However, bilastine reduced baseline TSS significantly more than montelukast after the first and second weeks of treatment ($p < 0.05$).[28]

Experts' Opinions: Role and Positioning of Bilastine-Montelukast Combination in the Management of AR

(1) The experts mentioned that bilastine plus montelukast as a combination therapy is an attractive treatment option in a selective patient

population that requires both classes of drugs for achieving better results. They emphasized that in a group of patients with a hyperreactive airway disease such as asthma, this combination has an important role and may be used.

(2) The experts also opined that montelukast monotherapy or as a combination should be used for not more than 4 to 6 weeks.

Conclusion

Valuable insights have been obtained regarding the role and positioning of bilastine and bilastine plus montelukast combination in the management of AR and AR with concomitant asthma in adults and children based on an expert panel discussion in India. The experts opined that bilastine 20 mg is a good drug for the management of AR symptoms in adults and adolescents aged 12 years and above. More recently, bilastine has been approved widely for use in children aged 6 to 11 years. However, the experts suggested that more studies need to be conducted for evaluating the efficacy and long-term safety of bilastine in this subgroup of the patient population. Studies have shown that combination therapy of LTRAs plus oral H_1-antihistamines can increase the therapeutic efficacy against daytime and composite nasal symptoms, including rhinorrhoea, sneezing, and itching. Patients with perennial AR may benefit more from the combination therapy of LTRAs plus oral H_1-antihistamine compared with oral H_1-antihistamines alone. The synergistic combination of bilastine-montelukast therapy has a dual action on early- and late-phase allergic reactions in AR patients. As per the experts, bilastine plus montelukast as combination therapy is an attractive treatment option in a selective patient population (especially the patients with a hyperreactive airway disease such as asthma), which requires both classes of drugs for achieving better results.

Acknowledgements: We would like to thank BioQuest Solutions for the editorial assistance.

Authors' Contribution: All authors have contributed equally to the conception design, drafting, reviewing, and finalization of the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bhattacharya K, Sircar G, Dasgupta A, Bhattacharya SG. Spectrum of allergens and allergen biology in India. Int Arch Allergy Immunol 2018;177:219-37.
2. World Allergy Organization (WAO). White Book on Allergy. Available from https://www.worldallergy.org/UserFiles/file/WAO-White-Book-on-Allergy_web.pdf. Accessed on 16 July, 2021.
3. Chandrika D. Allergic rhinitis in India: an overview. Int J Otorhinolaryngol Head Neck Surg 2017;3:1-6.
4. Bousquet J, Khaltaev N, Cruz AA, *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA (2)LEN and AllerGen). Allergy 2008;63:8-160.
5. Dykewicz MS, Wallace DV, Baroody F, *et al.* Treatment of seasonal allergic rhinitis: An evidence-based focused 2017 guideline update. Ann Allergy Asthma Immunol 2017;119:489.e41-511.e41.
6. Varshney J, Varshney H. Allergic rhinitis: an overview. Indian J Otolaryngol Head Neck Surg 2015;67:143-9.
7. Hossenbaccus L, Linton S, Garvey S, Ellis AK. Towards definitive management of allergic rhinitis: best use of new and established therapies. Allergy Asthma Clin Immunol 2020;16:39.
8. Mösges R, Lee DL, Abong J, *et al.* Role of bilastine in the management of allergic rhinitis and urticaria: an Asia-Pacific consensus statement. Asia Pac Allergy 2016;6:56-66.
9. Rodríguez M, Vozmediano V, García-Bea A, *et al.* Pharmacokinetics and safety of bilastine in children aged 6 to 11 years with allergic rhinoconjunctivitis or chronic urticaria. Eur J Pediatr 2020;179:801-5.
10. Walekar A, Chodankar D, Naqvi M, Trivedi C. Assessment of bioequivalence of fexofenadine and montelukast fixed dose combination tablet versus separate formulations of the individual components at the same dose levels. Indian J Pharm Sci 2016;78:651-6.
11. Diamant Z, Mantzouranis E, Bjermer L. Montelukast in the treatment of asthma and beyond. Expert Rev Clin Immunol 2009;5:639-58.
12. Shyna KP, Kumari M, Krishnan K, Azeez VK. Clinical profile and skin prick test analysis in children with allergic rhinitis of North Kerala, India. Int J Contemp Pediatr 2018;5:372-6.
13. Bro ek JL, Bousquet J, Agache I, *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol 2017;140:950-8.
14. Tohidinik HR, Mallah N, Takkouche B. History of allergic rhinitis and risk of asthma; a systematic review and meta-analysis. World Allergy Organ J 2019;12:100069.
15. Jaggi V, Dalal A, Ramesh BR, *et al.* Coexistence of allergic rhinitis and asthma in Indian patients: the CARAS survey. Lung India 2019;36:411-6.
16. Wang XY, Lim-Jurado M, Prepageran N, Tantilipikorn P, Wang DY. Treatment of allergic rhinitis and urticaria: a review of the newest antihistamine drug bilastine. Ther Clin Risk Manag 2016;12:585-97.
17. Bosma R, van den Bor J, Vischer HF, Labaega L, Leurs R. The long duration of action of the second generation antihistamine bilastine coincides with its long residence time at the histamine H_1 receptor. Eur J Pharmacol 2018;838:107-11.
18. Church MK, Tiongco-Recto M, Ridolo E, Novak Z. Bilastine: a lifetime companion for the treatment of allergies. Curr Med Res Opin 2020;36:445-54.
19. Gandhi J, Godse K, Godse G. Bilastine: a novel antihistamine. Indian J Drugs Dermatol 2018;4:3-6.

20. Kawauchi H, Yanai K, Wang DY, Itahashi K, Okubo K. Antihistamines for allergic rhinitis treatment from the viewpoint of nonsedative properties. Int J Mol Sci 2019;20:213.
21. Horak F, Zieglmayer P, Zieglmayer R, Lemell P. The effects of bilastine compared with cetirizine, fexofenadine, and placebo on allergen-induced nasal and ocular symptoms in patients exposed to aeroallergen in the Vienna Challenge Chamber. Inflamm Res 2010;59:391-8.
22. Kuna P, Bachert C, Nowacki Z, *et al.* Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study. Clin Exp Allergy 2009;39:1338-47.
23. Sologuren A, Viñas R, Cordón E, *et al.* Open-label safety assessment of bilastine in elderly patients with allergic rhinoconjunctivitis and/or urticaria. Allergy Asthma Proc 2018;39:299-304.
24. Bartra J, Mullol J, Montoro J, *et al.* Effect of bilastine upon the ocular symptoms of allergic rhinoconjunctivitis. J Investig Allergol Clin Immunol 2011;21:24-33.
25. Okubo K, Gotoh M, Asako M, *et al.* Efficacy and safety of bilastine in Japanese patients with perennial allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study. Allergol Int 2017;66:97-105.
26. Novák Z, Yáñez A, Kiss I, *et al.* Safety and tolerability of bilastine 10 mg administered for 12 weeks in children with allergic diseases. Pediatr Allergy Immunol 2016;27:493-8.
27. Liu G, Zhou X, Chen J, Liu F. Oral antihistamines alone vs in combination with leukotriene receptor antagonists for allergic rhinitis: a meta-analysis. Otolaryngol Head Neck Surg 2018;158:450-8.
28. Lavorini F, Matucci A, Rossi O, Pistolesi M, SKY study investigators. Concomitant bilastine and montelukast as additive therapy for seasonal allergic rhinoconjunctivits and mild-to-moderate asthma.The SKY study. Allergy 2020;75:675-7.
29. Paggiaro P, Bacci E. Montelukast in asthma: a review of its efficacy and place in therapy. Ther Adv Chronic Dis 2011;2: 47-58.
30. Diamant Z, Mantzouranis E, Bjermer L. Montelukast in the treatment of asthma and beyond. Expert Rev Clin Immunol 2009;5:639-58.
31. Karonen T, Neuvonen PJ, Backman JT. CYP2C8 but not CYP3A4 is important in the pharmacokinetics of montelukast. Br J Clin Pharmacol 2012;73:257-67.
32. Gray N, Howard A, Zhu J, Feldman LY, To T. Association between inhaled corticosteroid use and bone fracture in children with asthma. JAMA Pediatr 2018;172:57-64.
33. Benard B, Bastien V, Vinet B, Yang R, Krajinovic M, Ducharme FM. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. Eur Respir J 2017;50: 1700148.
34. van Adelsberg J, Philip G, Pedinoff AJ, *et al.* Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period [published correction appears in Allergy 59 (3):357]. Allergy 2003;58:1268-76.
35. Virchow JC, Bachert C. Efficacy and safety of montelukast in adults with asthma and allergic rhinitis. Respir Med 2006;100:1952-9.