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Review Article

Bilastine - Novel anti histamine drug for allergic rhinitis

Abhijit Trailokya[1],*, Soumen Roy[1]

[1] *Medical affairs Alkem Labs Mumbai, Mumbai, Maharashtra, India*

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ABSTRACT

The immune system is a fundamental part of human protection against infection and disease.
The immune system can occasionally lead to unfavourable reactions in the host which are known as hypersensitivity reactions. The exaggerated immune reactivity (hypersensitivity) to certain environmental substances (allergens) like airborne pollens, dust, mites, pet dander, and reactions to certain foods that normally have little effect on most people is known as allergy. The incidence of allergic disease like allergic rhinitis (AR), food borne allergy, asthma and anaphylactic reactions are prevalent in 25% of populations predominately in adolescents and adults in industrialised countries. Bilastine is a novel second-generation non-sedative, highly selective histamine H1 receptor antagonist that suppresses some allergic inflammatory processes that inhibits the release of histamine from mast cells and is approved in the treatment allergic rhinitis, urticaria and pruritus associated with skin diseases. This review covers the safety, efficacy and pharmacological aspects of Bilastine as an important product for treatment of allergic rhinitis.

1. Introduction

Allergic rhinitis (AR) is an inflammatory disorder of nasal mucosal, induced by an allergen which triggers Ig-E mediated inflammation. Worldwide around 10-40% of the population across age group is affected by AR, which significantly affects the quality of life. AR is often underdiagnosed and overlooked by the physicians and well as patients and its severity is directly linked to conjunctivitis and asthma. [1,2]

2. Global Burden of Allergic Rhinitis

Worldwide prevalence of AR is around 10-40% among children and adults. Among 40% prevalence, gender wise 15% men an 14% female were affected as per the Scandinavian studies and European community respiratory health survey. Severe AR symptoms in children was found in African and American populations. Prevalence and disease burden varies among countries which may be due to geographic variations and difference in the nature of allergens burden. In India, the prevalence of AR is 30% among the populations. [3,4] In developed and industrialized countries, 25% populations, especially children and young adults are affected by allergic disease such as AR, hay fever, allergic asthma, food allergy, allergic skin inflammation and anaphylaxis. [5]

2.1. Allergic rhinitis: Classification according to ARIA guideline 2019

AR is an inflammation of nasal mucosa that causes elicit immune response to Ig-E mediated inflammation by production of immune mediators like histamines. [6] The Allergic Rhinitis and its Impact on Asthma (ARIA) classification was first proposed in 1999; which provided a medium for describing and classifying AR by considering

* *Corresponding author*.
E-mail address: abhijit.trailokya@alkem.com (A. Trailokya).

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both severity of symptom and duration. The standard classification of AR was updated by ARIA in 2019. ARIA is classified based on the nature of the symptom and severity. AR is considered serious "if it is a persistent allergic rhinitis" in which the symptoms occur "at least 4 days a week and over a period of at least 4 weeks" and must therefore be classified as severe (Figure 1).[6]

Second generation H_1 antihistamine medications are preferred over first generations because of its effectiveness in managing allergic symptoms without side effects of sedation and muscarinic receptor blockage which is found in first generations. Among the second generations, non-sedating H_1 antihistamine medication are better in managing the allergic symptoms daytime without sedations. The pathophysiology of allergy involves cascade of inflammatory reactions that sensitize the immune cells like eosinophils and lead production of Ig-E antibody which destabilize the mast cells and basophils to release inflammatory mediators such as histamines, leukotrienes, chemokines, cytokines and leads to inflammation. Antihistamine medication suppress the inflammatory processes and thereby leads to symptomatic relief from allergy.[7]

2.2. Management of allergic rhinitis

ARIA 2019 highly recommends use of oral H1-antihistamine and an INCS for the management of mild to severe intermittent and persistent symptoms of allergic rhinitis.[6] Bilastine and Fexofenadine are the preferred oral H1 receptor antagonists according to the AR and its impact on asthma (ARIA) guidelines.[8,9]

Non-sedating second-generation H1 antihistamines compared to Bilastine.

2.3. Effect of antihistamine drugs in cognitive psychomotor performance, and driving ability:

Safety of the drug in performing cognitive and psychomotor function such as driving vehicle is critical hence a non-sedative property is need to be taken into account in the rational selection of a second-generation antihistamine. Bilastine is a non-sedating antihistamine with fast adsorption. Bilastine does not get metabolised by liver enzymes and hence has few drug interactions as compared to other antihistamines. The benefit-to-risk ratio of Bilastine is optimal and it meets all conditions for contributing for safety in drivers requiring antihistamines; hence, it may be considered as an antihistamine of choice for use in drivers. Bilastine is recommended in the "Guidelines for the Handling of the Drugs Used for Aircraft Crew" prepared recently by the Ministry of Land, Infrastructure, and Transport of Japan.[10,11]

2.4. Bilastine - drug profile

Bilastine is a newer 2^{nd} generation H1 receptor antagonist drug approved for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU) in patients older than 12 years of age. AR is very common clinical manifestations in patients which is the most frequent reasons for the visit to their general practitioner or an ENT specialist. H1-antihistamines are the medications recommended by ARIA guidelines as a first line treatment for AR.[12]

3. Pharmacology

Bilastine is a non-sedating and a potent specific H1-antihistamine activity belongs to the second-generation piperidine class of drug. Bilastine supresses the eosinophil migration to the inflamed tissue and thereby stabilizes the mast cells. Bilastine is an H1 receptor inverse agonist. Bilastine has high specificity for H1-receptors. Bilastine exhibits 6 times and 3 times greater affinity for H1 receptor than fexofenadine respectively. Bilastine inhibits release of histamines, interleukin-4, and tumor necrosis factor-α from human mast cells and granulocytes and thereby exhibits anti-inflammatory activity as per the in vitro study. The efficacy of Bilastine (20mg) on rapid onset of action in reducing symptoms was 1 hour after intake was similar and non-inferior to cetirizine (10mg) and fexofenadine (120mg). Bilastine exhibits prolonged duration of action (26 hours after intake) compared to cetirizine and fexofenadine. Rapid onset of antihistamine effect (approximately 30 min). Maximum effect (60-65%) in the time range of 0.5 - 8 h.[8–12]

3.1. Mechanism of action

Bilastine is a selective histamine H1 receptor antagonist. In allergic reactions the sensitized immune cells release Ig-E antibody which binds to mast cells and destabilize them by releasing histamines and other inflammatory mediators which leads to symptoms of AR. Bilastine binds to H1 receptors of the mast cells and prevent destabilization and release of histamines and thus provides symptomatic relief from AR.[13]

3.2. Indication

For symptomatic relief of nasal and non-nasal symptoms of seasonal AR in patients 12 years of age and older and for symptomatic relief in CU in patients 18 years of age and older.[13]

4. Pharmacokinetics

Absorption: The bioavailability of Bilastine is 61% with Tmax 1.13 hour. Cmax reduces by 25-33% when taken low fat/high fat meal compared to fasting state. Bilastine does

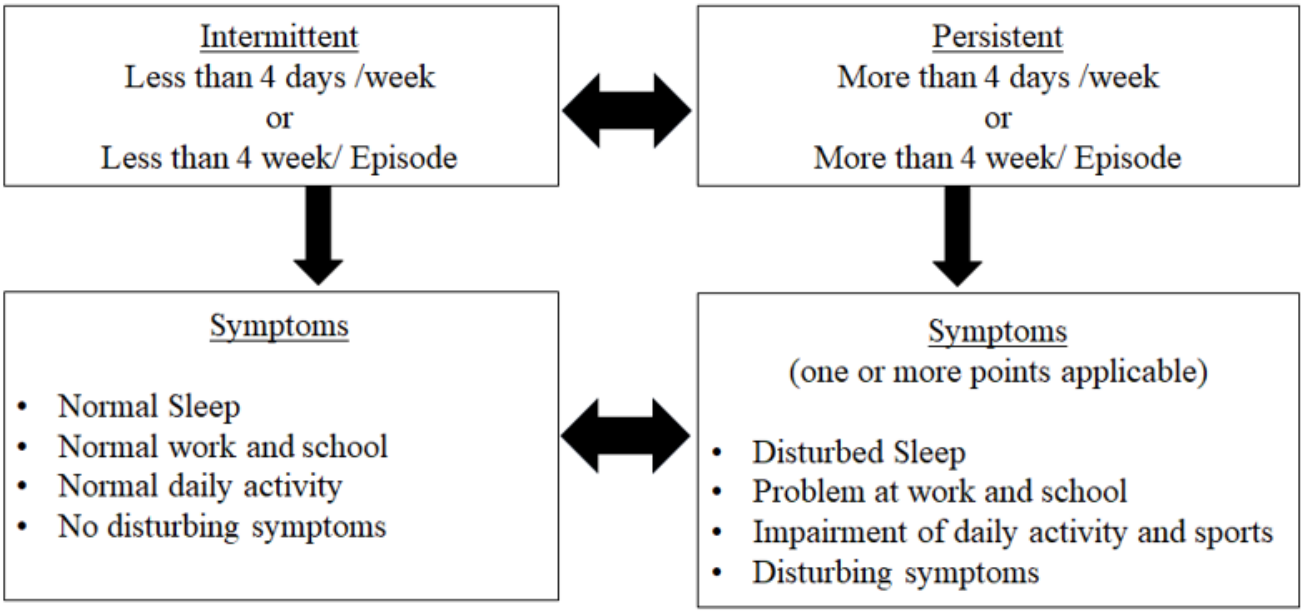

Fig. 1: Classification of the Allergic Rhinitis according to ARIA guideline 2019

Table 1: Comparison ofBilastine with second generation non-sedating antihistamines

Characteristics	Bilastine	Fexofenadine	Levocetrizine
Indicated for allergic rhinitis	Yes	Yes	Yes
Renal impaired patient requires dosage adjustment	No	No	Yes (in moderate-to-severe)
Dosage adjustment in hepatic impairment?	No	No	Yes (for concomitant moderate-to-severe renal impairment)
Dosage adjustment in elderly?	No	No	Yes (for concomitant moderate-to-severe renal impairment)
Drug interactions which are clinically relevant	No	Yes (antacids)	Unlikely (no available data)
Interaction with alcohol?	No	Not mentioned	Caution
Antihistamine properties with ARIA recommendations	10	9.5	6.5

not exhibit clinically relevant drug interactions unlike other second generation antihistamines as it does not interact with cytochrome P450 system. [12]

4.1. Distribution

The binding of Bilastine to plasma proteins is 84%–90%. Bilastine (20mg) exhibits volume of distribution (Vda) of 1.29L/Kg which is central compartment (59L) and peripheral compartment (30L) No tissue accumulation was found after single or multiple doses of Bilastine. Bilastine exhibits the estimated half-life of 14.53 hours.

4.2. Route of elimination

Bilastine is excreted majorly from faecal route (66.5%) followed by urine (28.3%) as unchanged parent compound with total clearance of 9.20 L/hour.

4.3. Adverse effects

Headache, drowsiness, dizziness, and fatigue are the most common adverse events reported by patients with an incidence similar to placebo

Dosage and administration: Bilastine (20 mg) once daily dosage. For better results to be taken at least 1 h before or 2 h after the intake of meal.

No dose adjustment is required in patients over 65 years. In renal impaired patients, Bilastine dose reduction is not needed however concomitant administration of Bilastine and P-gp inhibitors must be avoided in patients with moderate to 'severe renal impairment. Since Bilastine is not metabolized in liver and its main route of elimination is renal, it does not seem likely that hepatic impairment could lead to Bilastine bioavailability in excess of its safety range. For these reasons, it is not necessary to make dose adjustments in patients with hepatic impairment. Safety and

efficacy of Bilastine in children below 12 years has not been determined. Bilastine is pregnancy category B drug. [14]

5. Safety and Tolerability

Safety and tolerability were established by all clinical studies. The most common adverse events reported by patients are Headache and lethargy. Bilastine does not prolong the QT/QTc interval and it does not cause significant changes on ECG at the studied doses, even in the case of interaction with drugs that increase its plasma levels, such as Ketoconazole. Bilastine does not cross the blood–brain barrier and thereby exhibits no sedation. At therapeutic doses, Bilastine does not have anticholinergic effects and does not affect psychomotor performance or enhance the effects of alcohol or the benzodiazepine and lorazepam. In on the road driving test studies, Bilastine does not show significant differences versus placebo. [10–14]

6. Clinical Evidences from ENT Prospective

Kuna P et al., (2009) in the randomized double blinded placebo-controlled study evaluated the safety and effectiveness of Bilastine 20mg and cetirizine 10mg in patients with seasonal allergic rhinitis (SAR). Total of 683 patients with SAR; with the age group of 12 to 70 years were randomly administered with Bilastine 20mg, cetirizine 10mg or placebo; OD for 2 weeks treatment. Patients with Bilastine and cetirizine exhibited significant improvement ($P<0.001$) in the mean total symptom scale (TSS) as compared with placebo. Bilastine 20mg OD was found to be non-inferior to cetirizine 10mg but significantly superior to placebo in symptomatic relief from SAR. In safety profile, significantly cetirizine treated patient's experienced higher episodes of somnolence and fatigue. [15]

The effectiveness of Bilastine, cetirizine and fexofenadine in symptomatic relief from allergic rhinitis was evaluated in a double blind study by Horak F et al., (2010). Total of 75 volunteered patients allergic to grass pollens were exposed for 2 consecutive days to develop symptoms of AR. Bilastine 20 mg, cetirizine 10 mg, fexofenadine 120 mg, or placebo were taken orally (2 hour) after the start of provocation on day 1.Total nasal symptom scores (TSS) of the symptoms of AR was assessed on day 1 and 2. There was significant reduction in the TSS of AR such as nasal secretion and eye symptoms. Bilastine and Cetirizine had a rapid onset of action, within 1 h, and a long duration of action which was more than 26 hours. Fexofenadine was non-inferior on day 1 but was less effective on day 2, indicating a shorter duration of action. Safety and tolerability was found to be similar for Bilastine, cetirizine and fexofenadine. [16]

7. Summary

Bilastine is a 2^{nd} generation H1 receptor antagonist indicated for allergic rhinitis and chronic urticaria in patient above 12 years of age. Bilastine has high specificity and affinity (3-6 fold) for H1receptors as compared to cetirizine and fexofenadine, respectively. Bilastine 20mg OD; best taken 1 hour before meal intake as per recommendations. Bilastine 20mg was non-inferior in efficacy to cetirizine 10mg and fexofenadine 120mg in symptomatic relief from AR and urticaria. Safety of Bilastine is established and superior in non-sedation compared to cetirizine and minimal drug interaction compared to fexofenadine. Bilastine suppresses histamine induced skin symptoms sooner after the administration and is also safe for use in major population. Bilastine was also found advantageous when compared with other second generation histamine H1 antagonists like fexofenadine and Cetrizine.

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9. Conflicts of Interest

The author declares no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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Author biography

Abhijit Trailokya, DGM (Medical affairs Alkem Labs Mumbai)

Soumen Roy, Medical Adviser (Medical affairs Alkem Labs Mumbai)

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