REVIEW ARTICLE

Allergic Rhinitis and Treatment Modalities: An Update

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Burden of Allergic rhinitis

Allergic rhinitis (AR) is an allergic disorder that is frequently encountered in primary care. It is a symptomatic condition of the nose caused by allergen exposure and IgE-mediated inflammation and characterised by presence of symptoms of nasal congestion, clear rhinorrhea, sneezing, postnasal drip, and nasal pruritus. It exerts a marked detrimental effect on the affected individual's sleep, social life, quality of life, and attendance and functioning at school and work. Apart from the nasal symptoms, patients with AR may also present with associated allergic conjunctivitis, non-productive cough, Eustachian tube dysfunction, and chronic sinusitis.[1-3] House dust mites, domestic animals, insects pollens and moulds and occupational triggers such as latex, tobacco smoke, are the triggers associated with allergic rhinitis occurrence.[3]

Epidemiology of Allergic Rhinitis

Allergic rhinitis, with a prevalence estimated at 10-30%, affects the lives of more than 500 million people worldwide. The burden is particularly high and increasing in Asia Pacific, where many people now live in overpopulated cities with high levels of environmental pollution.[1] The incidence of AR in the pediatric population is also quite high; epidemiological studies suggest that AR affects up to 25% of children, thus making it one of the most common chronic pediatric disorders.[2] According to data available from International Study for Asthma and Allergies in Childhood, 14.6% in the 13 to 14 year age group and 8.5% in the 6 to 7 year age group display symptoms of rhinoconjunctivitis associated with allergic rhinitis.[2] Due to global urbanization, prevalence of allergic rhinitis has increased gradually over the years.[4]

Allergic Rhinitis as a Risk Factor for Asthma

Asthma and allergic rhinitis often co-exist in the same patient and has been referred to as united airway disease as they both share an underlying systemic pathology. According to the epidemiological studies, majority of patients with asthma have concomitant rhinitis and the presence of rhinitis is an increased risk factor for development of asthma. It has been well known that patients with allergic rhinitis are at threefold increased risk of developing asthma; the risk being higher in patients with more severe and persistent rhinitis. Studies have shown that asthma is found in up to 38% of patients with AR and nasal symptoms are present in 6% to 85% patients with asthma. This co-existence may be due to the fact that such patients have higher FeNO, a lower FEV1, and greater bronchial hyper-reactivity along with presence of both genetic and environmental factors that may contribute to aggravating both the asthma and the rhinitis.[2,5,6]

Histamine and the H1-Receptor Subtype in Allergic Rhinitis

Histamine plays a vital role in the pathophysiology of allergic rhinitis. On exposure to allergen, specific antibodies of the IgE type are produced in genetically predisposed individuals, which interact with receptors on the surface

of basophils and mast cells, resulting in intracellular reactions and thus leading to exocytosis and the release of histamine and other inflammatory mediators such as platelet-activating factor and cytokines. This release of histamine results in receptor-mediated smooth muscle cell contraction in the gastrointestinal and respiratory tracts, sensory nerve stimulation, vasodilation, plasma extravasation, and cellular recruitment that may further lead to erythema, flushing, nasal congestion, and pruritus.[1]

Histamine mediated activity is not only seen in the early allergic response, but is also associated with late allergic response via stimulation of production of cellular adhesion molecules, class II antigens, and cytokines. Out of four histamine receptors, allergic response is primarily mediated by the H1 receptor subtype.[1]

Antihistamines are not competitive antagonists of histamine binding to H1 receptors; but, they bind to different sites from histamine on H1 receptors. Therefore, these antihistamines are inverse agonists rather than receptor antagonists. After binding to H1 receptors, they interfere with histamine action on sensory neurons and small blood vessels, directly downregulating allergic inflammation.[1]

Management of Allergic Rhinitis

Treatment of allergic rhinitis should lay focus on allergen avoidance, pharmacotherapy, and immunotherapy. Pharmaceutical management of AR rests on symptomatic treatment with antihistamines, nasal or oral glucocorticoids, nasal decongestants and leukotriene receptor antagonists. H1-antihistamines are widely preferred and utilized first-line medication to treat allergic rhinitis. However, first generation of antihistamines such as diphenhydramine and hydroxyzine are no longer recommended due to various adverse side effects impacting the central nervous system, anticholinergic side effects and cardiac toxicity.[3,4]

For an antihistamine to be effective and safe, it should fulfill the criteria for an ideal antihistamine as showcased in Table 1.[1]

Table 1: Properties of an ideal antihistamine[1]

Pharmacological properties	Efficacy	Side effects	Pharmacodynamic
❖ Potent and selective activity at H1 receptors ❖ No pharmacokinetic interactions with food, medication, or intestinal proteins ❖ No interaction with cytochrome P450 ❖ No interaction with other diseases	❖ Effective in both intermittent and persistent allergic rhinitis ❖ Effective against all nasal symptoms, including obstruction ❖ Improves ocular symptoms	❖ No sedation or cognitive or psychomotor impairment ❖ No anticholinergic activity ❖ No weight gain ❖ No cardiac safety concerns ❖ Potential use in pregnancy and breastfeeding	❖ Rapid onset of action ❖ Long duration of action permitting once-daily dosing ❖ No potential for tolerance development (tachyphylaxis)

Bilastine: An Effective Antihistamine

Bilastine, a second-generation H1-antihistamine possess the highest number of desired characteristics of an ideal antihistamine and hence is been approved and widely used for the symptomatic treatment of AR and rhino-conjunctivitis (seasonal and perennial) and urticaria in adults.[1,7]

Bilastine has a high specific affinity for H1 receptors and possess both antihistaminic as well as anti-inflammatory properties. It has a favourable pharmacokinetic profile, gets rapidly absorbed resulting in an onset of clinical effect within one hour of administration, and has a long duration of action, exceeding 24 hours, which allows for once-daily dosing.[7,8]

Box 1: Properties of bilastine[1,7-10]

- Potent and selective activity at H1 receptors
- Rapid onset and long duration of action
- Lack of sedation and cognitive impairment
- Does not affect psychomotor performance or driving performance
- Does not interact with alcohol or lorazepam
- No cardiac safety concerns, and no potential for tachyphylaxis
- Does not undergo presystemic hepatic metabolism
- Does not interact with the cytochrome P450 system
- Unlikely to be involved in drug-drug interactions
- Exerts anti-inflammatory actions beyond its antihistaminic effects

Bilastine is well tolerated, non-sedating H1 receptor inverse agonist. Its non-sedating property could be linked to the fact that bilastine is a substrate for P-glycoprotein, an organic anion transporting protein (OATP) that prevents its uptake across the blood brain barrier into the brain, limiting the likelihood of central nervous system (CNS) effects such as sedation. Furthermore, bilastine neither exerts impact on CYP450 enzyme of liver nor it does have any drug interaction.[8,9] Moreover, there is no associated weight gain, anticholinergic effects, or cardiac side effects with bilastine. When administered at supratherapeutic doses, it exerts no significant effect on QT interval, even when administered with ketoconazole. Table 2 highlights the properties of bilastine which makes it a promising treatment modality in allergic rhinitis.[1,7-10]

Efficacy of Bilastine in Allergic Rhinitis

A study[11] was done to evaluate the efficacy and safety of bilastine 20 mg as compared to cetirizine 10 mg and placebo in relieving the symptoms of seasonal allergic rhinitis. It was shown that total symptom score was significantly reduced in bilastine- and cetirizine-treated group as compared with placebo. Though all the treatments were well-tolerated, adverse event profile of bilastine was significantly better with fewer patients reporting somnolence and fatigue as compared to patients in the cetirizine-treated group (Figure 1).

In a recent study[8] done by Abha Kumari and collegues, effectiveness of bilastine and fexofenadine was compared in treatment of allergic rhinitis patients. It was shown that bilastine was significantly more effective than fexofenadine in reducing total nasal symptom score and thus the quality of life of patients affected (Figure 2). The reduction in total nasal symptom score was first seen within 24 hours and was maintained till 2nd week; signifying that bilastine is superior to fexofenadine in treating patients with allergic rhinitis.

Devendra S *et al* conducted a study[12] to evaluate and compare the efficacy and safety of bilastine 20 mg and levocetirizine 5 mg in the treatment of allergic rhinoconjunctivitis. It included 100 patients with chronic rhinocojunctivitis. It was shown that though both bilastine 20 mg and levocetirizine 5 mg significantly reduced the TSS on the 7th and 14th post-treatment days (Figure 3); bilastine was well-tolerated, with fewer patients reporting adverse events as compared to patients in the levocetirizine group.

Figure 2: Mean total nasal symptom score at baseline, after 24 hour, after 1 week and after 2 weeks of treatment with bilastine and fexofenadine[8]

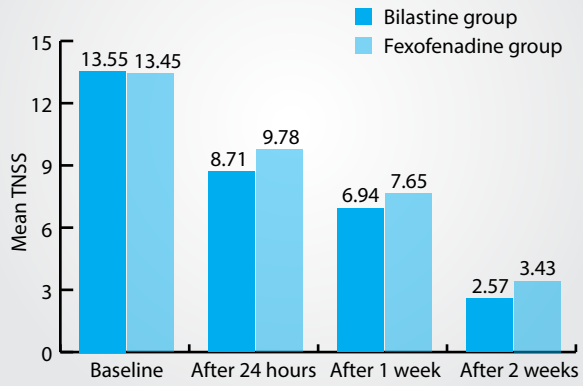


Figure 1: Proportion of patients with seasonal allergic rhinitis who showed better tolerability profile with bilastine as compared to cetirizine[11]

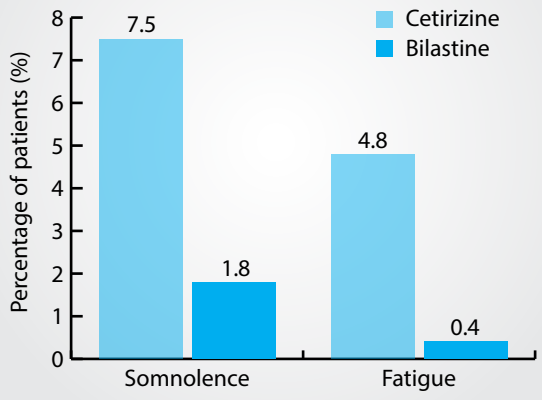


Figure 3: Effect of bilastine versus levocetirizine on total symptom score in patients with allergic rhinoconjunctivitis[12]

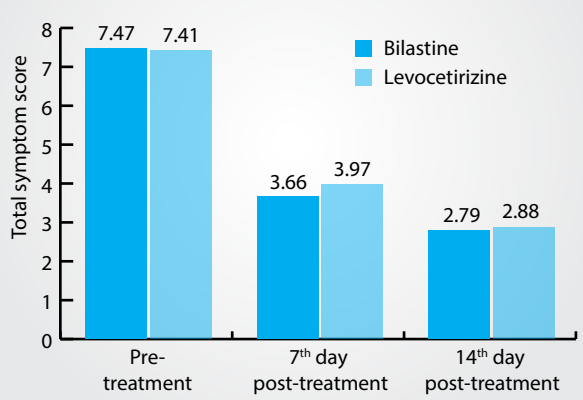
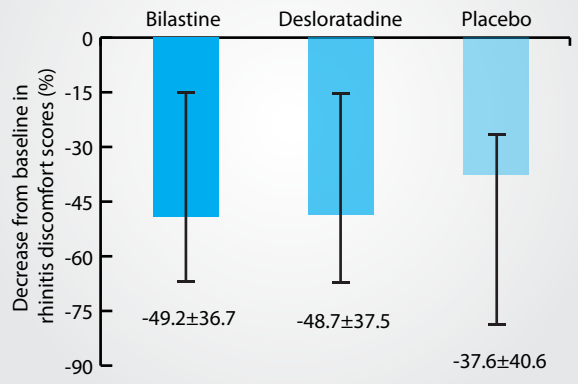


Figure 4: Decrease from baseline in rhinitis discomfort scores with bilastine versus desloratadine versus placebo in patients with seasonal allergic rhinitis



A study[13] was conducted to compare the efficacy and safety of a single daily dose of 20 mg bilastine vs placebo and desloratadine 5 mg in patients with seasonal allergic rhinitis. It was shown that bilastine 20 mg progressively improved the symptoms of allergic rhinitis from baseline levels over a period of 2 weeks. The AUC of total symptom score was decreased to a greater extent from baseline in the bilastine 20 mg-treated group versus the placebo-treated and the desloratadine-treated group. At day 14, bilastine 20 mg led to markedly greater decreases from baseline in mean rhinitis discomfort scores, compared with placebo and desloratadine 5 mg (Figure 4). Bilastine 20 mg improved the QOL of patients, as measured by the rhinoconjunctivitis quality of life questionnaire (RQLQ). Thus, it could be concluded that although bilastine and desloratadine were equally efficacious in the treatment of SAR, bilastine may have a slightly more favorable safety profile.

In another study[14] done in patients with perennial allergic rhinitis, it was shown that bilastine 20 mg administered once daily for 2 weeks exhibits a rapid onset of action and may offer an effective and well-tolerated therapeutic option in such patients. Similarly, bilastine and cetirizine were similarly effective; and more effective than placebo, during a 4-week treatment period in patient's with PAR. Moreover, bilastine was found to be safe and well-tolerated over a 1-year treatment period.[15]

Conclusion

Allergic rhinitis is an allergic disorder that is frequently encountered in primary care wherein histamine plays a vital role in its pathophysiology. Treatment of allergic rhinitis should lay focus on allergen avoidance, pharmacotherapy, and immunotherapy. Bilastine, a second-generation H1-antihistamine possess both antihistaminic as well as anti-inflammatory properties and has a long duration of action, which allows for once-daily dosing. Bilastine is an effective, non-sedating and well-tolerated treatment option for patients with allergic rhinitis and hence can be considered as a first-line of treatment in such patients.

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