Role of Antihistamine and Leukotriene Receptor Antagonist in Allergic Rhinitis Management: Newer Perspectives

Dr. Manish Maladkar[1], Dr. Shrikant Patil[2], Sonal Kamble[3]

Abstract

Allergic disorders are conditions induced by the immune system's hypersensitivity to normally harmless chemicals known as allergens. The most common allergens include dust mites, pollution, grass pollens and food allergens such as milk, egg, soy, wheat, nut, or fish proteins. Allergic diseases include allergic rhinitis (AR), allergic asthma, urticaria, atopic dermatitis, contact allergies and food allergies. AR is the most common of all atopic diseases, afflicting 10%–30% of adults and up to 40% of children all over the world. The mechanisms underlying AR are highly complex and involve multiple immune cells, mediators and cytokines such as histamine and leukotrienes. It is characterized by nasal symptoms such as sneezing, nasal itching, rhinorrhea, and nasal congestion. It is also, associated with non-nasal symptoms such as watery eyes, redness in the eyes or inflammation. It has a significant effect on one's health, as well as the quality of one's sleep, work productivity and academic performance. The management of AR includes allergen avoidance, pharmacotherapy, and immunotherapy. Complete avoidance of allergens that trigger AR symptoms is not possible. Current pharmacologic options include antihistamines (oral and intranasal), Leukotriene Receptor Antagonists (LTRAs), Intranasal Corticosteroids (INCS), decongestants and oral and intranasal anticholinergics. Amongst other antihistamines, Bilastine has emerged as a new, non-sedating and well-tolerated antihistamine while Montelukast is an effective add-on LTRA option to an antihistamine with well-established literature in the management of moderate-severe AR. Immunotherapy is a treatment option for patients who have not responded to medication.

Keywords: Allergic rhinitis, antihistamines, LTRAs, montelukast, bilastine

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Introduction

Allergic Rhinitis, the most common type of chronic rhinitis, is an IgE-mediated symptomatic inflammatory disorder of the nasal mucosa. It is caused by an infiltration of eosinophils, T cells, mast cells, and basophils that releases several mediators such as histamine, leukotrienes, chemokines, and cytokines.[1]

AR and asthma co-exist in a substantial percentage of patients. More than 40% of patients with AR have asthma, and 30-80% of asthmatic patients suffer from concomitant rhinitis.[2] Other co-morbidities that are observed in patients with AR include rhinosinusitis, nasal polyposis, upper respiratory infections, otitis media with effusion, Eustachian tube dysfunction, sleep impairment, obstructive sleep apnea, hyposmia and bronchial hyper-reactivity.[2,3]

Allergic Diseases: A Global Public Health Issue

The global prevalence of allergy disorders is increasing substantially in both developed and developing countries. The World Health Organization has estimated that 400 million people in the world suffer from AR and 300 million from asthma.[4]

The Burden of Allergies in India

AR is a global health issue that causes significant suffering and disability. In India, the prevalence and severity of allergic diseases are on the rise. In the Asia-Pacific region, the prevalence of the disease among adults ranges from 20% to 30%.[5]

Impact on Quality of Life due to Allergic Rhinitis and its Associated Co-morbidities

AR is a long-lasting condition that has a significant impact on the quality of life (QOL) of patients. It usually goes undetected in the primary care setting, which further complicates the condition. The presence of AR has been associated with numerous comorbid disorders, including asthma, chronic otitis media, rhinosinusitis, and oropharyngeal lymphoid hypertrophy, with secondary obstructive sleep apnea and disordered sleep. Poorly controlled AR can trigger exacerbations of these co-morbidities because they often share pathophysiologic (inflammatory) pathways in common with AR. The accompanying co-morbidities have a significant influence on the quality of life, restricting work and school performance, altering sleep quality, and hindering social and everyday life activities. As the Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations emphasize, asthma and AR usually co-exist and should be considered simultaneously when discussing treatment choices with patients. The main goal of treating patients with AR is to control symptoms while maintaining function and improving the patient's QOL.[3,6]

Pathophysiology

AR has convoluted pathophysiology that includes an allergic reaction in both the early and late stages. The allergic cascade is triggered by allergens such as pollens, dust mites, animal dander, and a variety of other allergens, which are further recognized by antigen-specific immunoglobulin E (IgE) receptors on mast cells and basophils in sensitized individuals.[7]

Early-Phase Reaction

When AR patients are exposed to allergens, allergic reactions occur in 2 different patterns as per time sequence. The early-phase reaction is characterized by mast cell degranulation and is associated with the rapid onset (within minutes) of acute nasal symptoms (i.e., sneezing and rhinorrhoea) and the emergence of ocular symptoms (i.e., itching, redness, and watery eyes). These symptoms are caused by the release of the principal mediator of early-phase reaction i.e., histamine, particularly from mast cells in the nasal mucosa. This reaction is triggered by allergen deposition and elution into the mucus layer, where the allergens are picked up by antigen presentation cells and processed before being presented to helper T lymphocytes. Helper T cells that have been activated release cytokines such as IL-4 and IL-13 and interact with B lymphocytes to cause the production of allergen-specific IgE. Following that, allergen-specific IgE binds to an IgE receptor on the surface of mast cells with a high affinity. Upon cross linking, mast cells degranulate and release various pre-formed and newly formed mediators leading to the early-phase reactions. Stimulated mast cells induce nasal symptoms by secreting chemical mediators such as histamine, prostaglandins, and leukotrienes. Histamine stimulates the sensory nerve endings and mucous glands, thereby inducing sneezing and rhinorrhea, respectively. In addition, they act on the blood vessels causing nasal congestion together with the other potent pro-inflammatory cytokines (e.g., leukotrienes) and eicosanoids (e.g., prostaglandins and kinins). They also increase vascular permeability, leading to edema formation.[7,1]

Late-Phase Reaction

The early-phase response is usually followed by the late phase response, which occurs 4-6 h after antigen stimulation. The late-phase response is mediated by leukotrienes, kinins, and histamine which re-

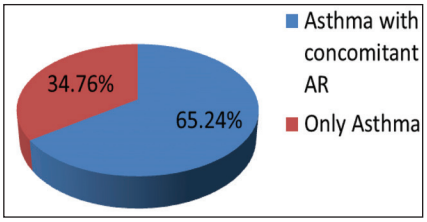
Table 1: Mediators of inflammation in the early and late-phase[1]

Early Phase Mediators	Effects
Histamine	Sensory nerve stimulation- sneezing and itching, gland secretion- rhinorrhea, vascular permeability, smooth muscle contraction
Leukotrienes	Nasal congestion, Smooth muscle contraction, vascular permeability, neutrophil, eosinophils chemotaxis
Late Phase Mediators	
Leukotrienes	Sustained Inflammation and Prolonged symptoms
Eosininophils	Influx of inflammatory cells
Platelet Activating Factors, TNF-α, IL-1, IL-5, IL-8	Mucus secretion, Airway permeability, Chemotaxis, Vascular permeability

sults in the prolongation of symptoms such as sneezing and rhinorrhea but most predominantly sustained nasal congestion which lasts for about 18-24 h. Also, it is characterized by an inflammatory cellular influx comprising predominantly T lymphocytes, basophils, and eosinophils resulting in nasal obstruction which is the hallmark of the allergic response (see Table 1).[1]

Allergic Rhinitis and Asthma: A Clinical Challenge

AR is linked to an increased chance of acquiring asthma. Patients with AR are three times more likely to develop asthma.[8] The CARAS study, an Indian survey, reported the co-morbidity of AR in asthma patients with a high incidence of 65.24%.[9] The relationship between the upper and lower airways, as well as the concept of one airway one disease, has been explained by several mechanisms including genetic factors, anatomic links and neural interaction between the upper and lower airways.[10]



Clinical Classification

The first-ever evidence-based guidelines, ARIA recommends a new classification (see Figure 1) for AR which considers both the duration (intermittent or persistent) and severity (mild, moderate-severe) of AR. As per the guideline, intermittent AR lasts for less than 4 days per week or less than 4 consecutive weeks, and persistent AR lasts for more than 4 days/week and more than 4 consecutive weeks. Patients are classified as mild AR patients if they have no sleep impairment and are able to undertake routine activities (including work or school). In moderate/severe allergic rhinitis, sleep and daily activities are disrupted.[11]

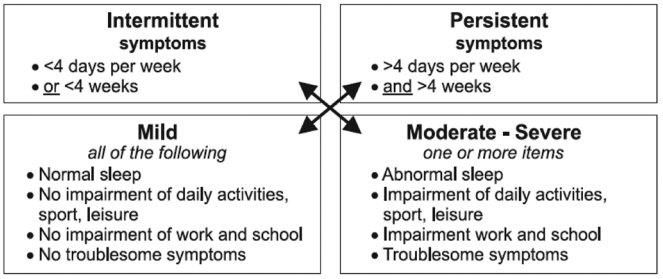


Figure 1: Allergic Rhinitis Classification based on symptom duration and severity.

Diagnosis and Investigations

Allergic rhinitis is frequently a long-term illness that goes undetected by primary care physicians. The diagnosis of AR is often made on the basis of clinical characteristics and response to pharmacotherapy.[3] A comprehensive history and physical examination are essential in determining the diagnosis of allergic rhinitis. Amongst all intradermal allergy tests, skin prick test (SPT) is the one that is most commonly used.[11] SPT is quick, inexpensive, and a minimally invasive way to confirm or rule out allergies. The in vitro detection of specific IgE antibodies is a useful complementary tool for diagnosing type I allergy, particularly in people who are unable to undergo SPT.[12]

Management of Allergic Rhinitis

Management of AR requires a stepwise approach depending on the severity and duration of symptoms. The purpose of treatment for AR is to alleviate symptoms and prevention of disease progression and treatment complications.[3] There are three approaches for managing AR which include allergen avoidance, pharmacotherapy, and immunotherapy.[13]

Allergic Rhinitis and its Impact on Asthma (ARIA) Guideline Recommendations

The most widely used guidelines for allergic rhinitis are the evidence-based ARIA guidelines. Figure 2 depicts a simple, step-by-step methodology for the treatment of allergic rhinitis. As per the guidelines, mild intermittent allergic rhinitis can generally be managed effectively with monotherapy such as oral antihistamines and/or decongestants or intranasal AHs or LTRA. In moderate-severe intermittent allergic rhinitis, a combination may be considered e.g., Oral or Intranasal AHs and decongestant or LTRA or INCS.

Similarly, for the patient suffering from mild persistent symptoms, the choice of treatment depends upon the severity and duration. It includes oral or intrana-

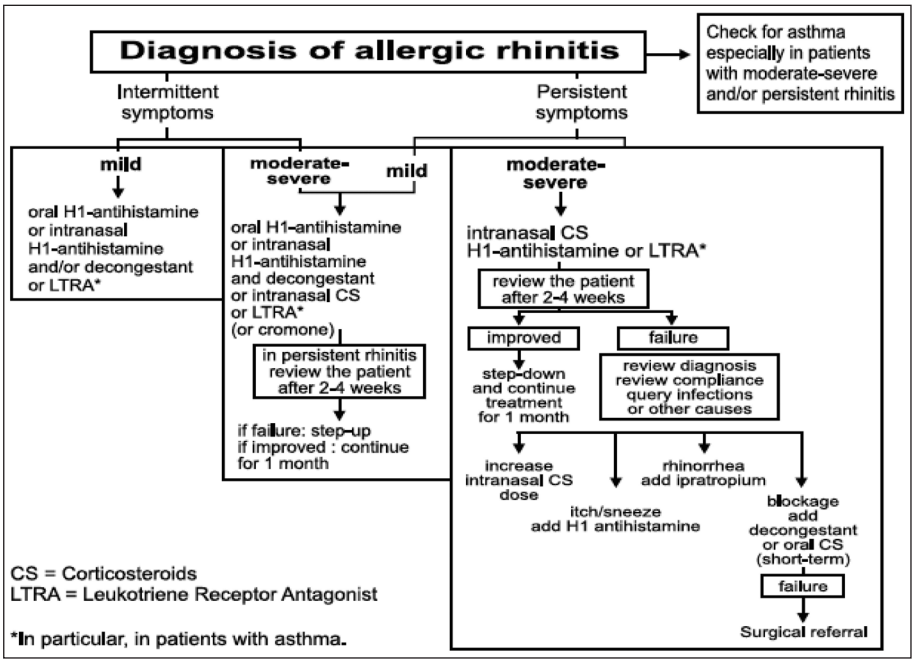


Figure 2: Algorithm for the management of Allergic Rhinitis[14]

sal AHs and decongestants or INCS or LTRA. In moderate-severe persistent allergic rhinitis, INCS, AHs or LTRA are preferred.[14]

Pharmacological Management of Allergic Rhinitis

Recommended drugs for AR management include oral /intranasal antihistamines (AHs), leukotriene receptor antagonists (LTRAs), intranasal corticosteroids (INCS) along with nasal decongestants, anticholinergics and oral corticosteroids in a particular group of patients. The most common pharmacologic treatment options include AHs, LTRAs and INCS. The rationale for treatment choice depends on the level of efficacy of the drugs and their affordable costs (see Table 2).[3]

Oral Antihistamines

Histamine is one of the major mediators involved in the development of AR symptoms. Three histamine receptors are presently recognized, but the nasal effects of histamine are predominantly H1-mediated. H1-receptor antagonists reduce the clinical expression of nasal itching, sneezing, and rhinorrhea, but they have only a modest effect on nasal congestion. For decades, AHs were the most often used class of medicines in the treatment of AR. They remain the mainstay of pharmacotherapy for AR. There are two generations of oral antihistamines (first and second-generation AHs).[3,15,16]

First Generation Antihistamines

First-generation AHs, such as Chlorpheniramine, Diphenhydramine, and Hydroxyzine, are associated with adverse central nervous system (CNS) side effects, including sedation and mental impairment, as well as anticholinergic side effects such as dry mouth, dry eyes, urinary retention, and constipation. Side effects of first-generation AHs could be explained by two phenomena: (i) they have poor specificity for the H1 receptor and interact with other receptors, and (ii) they also cross the blood-brain barrier. As a result of significant adverse effects, usage of first-generation antihistamines is limited.[3,16]

Second Generation Antihistamines

Second-generation AHs are the preferred first-line for the treatment of AR. They represented a major enhancement in antihistamine development because they are mainly non-sedating with a better safety profile. The second-generation AHs (Levocetirizine, Fexofenadine, Bilastine) are safer than first-generation agents as they do not cross the blood-brain barrier (BBB) due to less lipophilicity. However, because of differences in drug specificity for active transporter proteins (e.g., P-glycoprotein [P-gP]) across the blood-brain barrier, some second-generation agents may enter the CNS to a greater extent than others. Cetirizine, Desloratadine, and Loratadine, especially at high dosages, are potentially more sedating than Fexofenadine, Levocetirizine, and Bilastine. Furthermore, they are highly selective for H1 receptors and are devoid of

Table 2: Pharmacological properties of common medication classes.

	Intranasal Steroids	Antihistamines	LTRAs	Nasal Decongestants	Oral Decongestants	Nasal Cromones	Nasal Ipratropium
Rhinorrhea	+++	++	+	-	-	+	+++
Sneezing	+++	++	+	-	-	+	-
Pruritus	+++	++	+	-	-	+	-
Congestion	+++	+	++	+++	++	+	-
Ocular Symptoms	++	++	++	-	-	-	-

+++, marked benefit; ++, substantial benefit; +, some benefit; -no benefit

anticholinergic activity.[3,16]

Safety of Newer Generation Antihistamines

Newer, second-generation AHs are more selective and are recommended, as they are effective with less sedation and anticholinergic side effects. Second-generation antihistamines can also be dosed once daily as opposed to the multiple doses required for first-generation antihistamines, with a rapid onset of action between 1 and 2 hours.[16]

Bilastine is a new second-generation antihistamine recently approved for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU). It has certain advantages over other antihistamines. It has limited CNS penetration and is devoid of sedation as compared to first-generation AHs. Bilastine has been shown to bind selectively to the histamine H1 receptors but has no or very low affinity for other receptors such as H2-, H3-, serotonin, bradykinin, muscarinic, and calcium receptors. Bilastine administration at 20 mg and 100 mg had no clinically significant impact on QTc. Thus, cardiac safety was confirmed at therapeutic and supra-therapeutic doses. It is efficacious in all nasal symptoms, including obstruction and eye symptoms in patients with allergic rhinoconjunctivitis.[17] It is anticipated that a single dose of Bilastine 20 mg shows no adverse effects on sleepiness or performance of tasks related to flying ability in pilots under simulated cabin pressure circumstances for up to 6 hours after administration. Thus, providing a safe therapeutic alternative for pilots suffering from allergic rhinitis. [18] Bilastine is well tolerated and once-daily treatment was effective in managing symptoms and improving the patient's QOL.[17]

Intranasal antihistamines

They have a faster onset of action and are effective even in patients who had previously failed to respond to oral antihistamine medication. Azelastine nasal spray, unlike other oral antihistamines, is effective in relieving nasal congestion, a particularly troublesome symptom for rhinitis patients. Azelastine nasal spray is well tolerated by both adults and children. The most prevalent side effect is a bitter taste, which appears to be connected with inappropriate dosing techniques, but this problem can be mitigated by using proper dosing techniques.[16,19]

Intranasal corticosteroids

They are recommended as first-line therapy in moderate-severe AR and are the most effective medication for controlling AR symptoms. They can be used either alone or in conjunction with antihistamines. e.g. Fluticasone, Mometasone. They reduce nasal mucosal inflammation by lowering the release of inflammatory mediators and cytokines. They also reduce lower airway symptoms in patients with concurrent asthma and allergic rhinitis. When administered on a regular basis, they give symptomatic and effective relief. They are, however, most effective when used regularly, as the onset of action is 7 to 12 hours and the maximum impact is achieved in 2 weeks. Local side effects include epistaxis, nasal dryness, and (albeit uncommon) septal perforation, all of which are most likely caused by improper injection technique.[3,11,16]

Leukotriene Receptor Antagonist

The other major therapeutic class of drug as an add-on to AHs in the management of moderate-severe AR are the LTRAs, e.g., Montelukast. LTRAs inhibit the activity of cysteinyl leukotrienes (CysLTs), a powerful inflammatory mediator linked to nasal congestion, mucus formation, and inflammatory cell recruitment, all of which contribute to AR symptoms. The current ARIA guidelines recommend LTRA as an add-on therapy to antihistamines in patients with AR. Montelukast effectively improves the QOL by addressing the symptoms in patients with AR. They also reduce bronchospasm and attenuate the inflammatory response, thus may be useful in patients with concomitant asthma.[3,16]

Role of Bilastine and Montelukast in Allergic Rhinitis

When the pathophysiology of AR is examined, histamine is responsible for most of the symptoms of allergic rhinitis, including rhinorrhea, nasal itching, and sneezing. It has less of an effect on nasal congestion. Leukotrienes, on the other hand mainly cause increases in nasal airways resistance and vascular permeability. AHs and LTRAs are frequently used in the treatment of allergic rhinitis. Various studies have shown that newer second-generation antihistamine such as Bilastinewas more appropriate for patients whose cardinal symptoms are daytime rhinorrhea, pruritus, sneezing and nasal congestion, and LTRA such as Montelukast performed better for patients whose cardinal symptoms include difficulty going to sleep, night-time awakenings, and nasal congestion. Thus, inhibition of the mediators such as histamine and leukotrienes by Bilastine and Montelukast combination may provide enhancing and complementary effects, thereby reducing the symptoms effectively (see Table 3).[20]

Decongestants

In patients with AR, nasal congestion can be relieved by oral and intranasal decongestants (e.g., pseu-

Table 3: Bilastine and Montelukast proven efficacy in AR management.[21-25]

Study Reference	Age	No. of Participants	Subject	Indication	Comparators	Outcome Measures
Okuba K et al. 2016.	18-74 years	765	PAR	2-year or longer history of PAR	Placebo vs Fexofenadine vs Bilastine	TNSS
Kuna et al. 2009.	12-70 years	683	SAR	History of SAR for at least 2 years	Placebo vs Cetirizine vs Bilastine	NSS, NNSS, TSS
Bachert C et al. 2009.	12-70 years	720	SAR	History of SAR for at least 2 years	Placebo vs Bilastine vs Desloratadine	NSS, NNSS, TSS
Okuba K et al. 2016.	18-74 years	58-SAR 64-PAR	SAR, PAR	Patients with history of SAR/ PAR for at least 2 years	Placebo vs Bilastine	TNSS, TOSS, TSS
Rajput M S et al. 2020.	15-45 years	140	AR	History and physical examination consistent with a diagnosis of AR	Montelukast	TNSS
Philip G et al. 2002.	15-81 years	1302	SAR	History of SAR for atleast 2 years	Placebo vs Montelukast	Day-time/ night-time nasal symptoms score Daily composite (day-time nasal and night time) Daytime eye symptoms score

SAR-Seasonal Allergic Rhinitis , PAR-Perennial Allergic Rhinitis, NSS-Nasal Symptom Score, TNSS- Total Nasal Symptom Score, TSS-Total Symptom Score, TOSS-Total Ocular Symptom Score..

doephedrine, phenylephrine). However, the side-effect profile of oral decongestants (such as agitation, sleeplessness, headache, and palpitations) may limit their long-term use. They are contraindicated in patients with uncontrolled hypertension and severe coronary artery disease. The use of intranasal decongestants for an extended period of time increases the risk of rhinitis medicamentosa (rebound nasal congestion); hence these medicines should not be taken for more than 3–5 days.[3,16]

Anticholinergics

Anticholinergic medications may be used in the presence of rhinorrhea, according to clinical evidence. It alleviates rhinorrhea, especially if it is neurogenic rather than inflammatory in nature. Other nasal symptoms are largely unaffected by it.[3]

Conclusion

AR has a significant health impact on patient's quality of life and a substantial economic burden on society. To complicate matters, this condition can be challenging to diagnose correctly, which is essential for proper treatment. Patients can remain symptomatic despite being treated with mono- or multiple-therapy regimens if they are not prescribed or used correctly. Finally, therapeutic response to medication will be most effective when these medications are tailored to the patient based on the severity of the condition and the clinical profile.

Currently, preferred combination therapies include Oral AHs with LTRA, Intranasal AHs with INCS, and INCS with nasal decongestants. They offer distinct advantages for the management of AR.

Bilastine and Montelukast are emerging as promising options for the management of AR. A fixed-Dose Combination (FDC) of AH and LTRA offers an effective option for those who do not get benefit from monotherapy. It provides better control over the day-time and night-time symptoms of AR. Also, the FDC of Bilastine and Montelukast improves QOL and patient compliance.

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