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Review on Bilastine and Montelukast Used In Treatment on Allergic Condition

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Abstract:

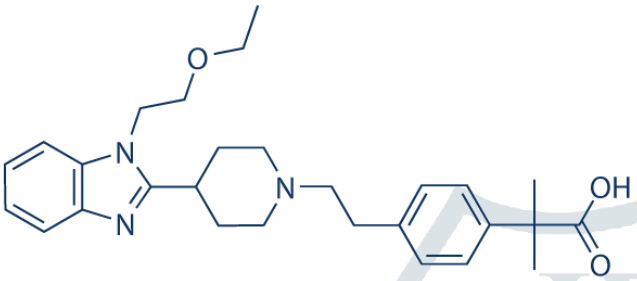
Allergic disorders are conditions induced by the immune system's hypersensitivity to normally harmless chemicals known as allergens. The most common allergens include dust mites, pollution, grass pollens and food allergens such as milk, egg, soy, wheat, nut, or fish proteins. Allergic diseases include 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

Introduction

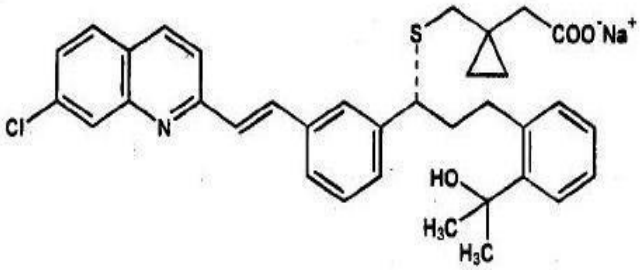
The frequency and impact of allergic diseases are often underestimated. [1]A key facilitator of the allergic response is immunoglobulin E (IgE) that is present on the surface of mast cells and basophils.[2] Interaction of the allergen with IgE and its receptor complex leads to activation of these cells and release of the substances, including histamine, that cause allergic symptoms. Because of the central role of histamine in allergic responses, many allergic conditions are treated with antihistamines, including allergic rhinitis and urticaria.[3,4] Antihistamines have been in clinical use for 70 years, and the pharmacological characteristics of these agents have been evolving over that time.Montelukast is a specific cysteinyl leukotriene receptor antagonist belonging to a styrylquinolines series with the chemical name 2-[1-[1(R)-[3-[2(E)-(7-chloroquinolin-2-yl) vinyl] phenyl]-3[2-(1-hydroxy-1-methylethyl) phenyl] propylsulfanylmethyl] cyclo-propyl] acetic acid sodium salt. It is mainly used to control and prevent symptoms caused by asthma (such as wheezing and shortness of breath) and

in allergic rhinitis. Bilastine is a new, well-tolerated, non-sedating H1 receptor antihistamine. Clinical studies have shown that Bilastine is as efficacious as other non-sedating antihistamines in allergic rhinoconjunctivitis and chronic urticaria in individuals from 12 and 18 years of age, respectively. Chemically it is, 2- [4-[2-[4-[1-(2-ethoxyethyl) benzimidazol-2-yl] piperidin-1- yl]ethyl]phenyl]-2-methylpropanoic acid. Drug Combination Bilastine and Montelukast Sodium were approved by CDSCO on 11th of March, 2020. Drug Combination Bilastine and Montelukast Sodium used for the treatment of allergic rhinitis and mild to moderate asthma [3,4,5].



BILASTIN

Figure 1



MONTELUKAST

Figure 2

Mechanism of action:

Montelukast:

Cysteinylleukotrienes (CysLT) like LTC4, LTD4, and LTE4, among others, are eicosanoids released by a variety of cells like mast cells and eosinophils.When such CysLT bind to corresponding CysLT receptors like CysLT type-1 receptors located on respiratory airway smooth muscle cells, airway macrophages, and on various pro-inflammatory cells like eosinophils and some specific myeloid stem cells activities that facilitate the pathophysiology of asthma and allergic rhinitis are stimulated.

In particular, CysLT-mediated airway bronchoconstriction, occluding mucous secretion, vascular permeability, and eosinophil recruitment are all types of effects that facilitate asthma.Alternatively, in allergic rhinitis, CysLTs are released by the nasal mucosa when exposed to allergens during both early and late phase reactions and participate in eliciting symptoms of allergic rhinitis like a congested nose and airway.

Subsequently, montelukast is a leukotriene receptor antagonist that binds with high affinity and selectivity to the CysLT type 1 receptor, which consequently assists in inhibiting any physiological actions of CysLTs like LTC4, LTD4, and LTE4 at the receptor that may facilitate asthma or allergic rhinitis.[6, 7]

Bilastine:

Bilastine is a selective histamine H1 receptor antagonist. During allergic response mast cells undergo degranulation which releases histamine and other substances. By binding to and preventing activation of the H1 receptor, bilastine reduces the development of allergic symptoms due to the release of histamine from mast cells.[8]

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, there- by reducing the symptoms effectively. [9]

Bilastine + Montelukast is a combination of two medicines:

Bilastine and Montelukast &Bilastine is an anti-allergic medication. It treats allergy symptoms such as itching, swelling, and rashes by blocking the effects of a chemical messenger (histamine) in the body. Montelukast works by blocking the action of leukotriene, a chemical messenger. This reduces inflammation in the airways to prevent asthma and relieve symptoms of allergies.[10]

Allergic Diseases: A Global Public Health Issue

The global prevalence of allergy disorders is in- creasing 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. 11]

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.[6] 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.[12]

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

The most widely used guidelines for allergic rhinitis are the evidence-based ARIA guidelines.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 for examble., Oral or Intranasal AHs and decongestant or LTRA or INCS.[13,14]

Chronic Urticaria.

Just one clinical study is available in urticaria. That was a double-blinded, placebo- controlled randomized, parallel-group, multinational study in 525 18-70 year old subjects with chronic idiopathic urticaria [9]. Inclusion criteria were a documented history of chronic urticaria occurring ≥3 times/week for 6 weeks and an individual urticaria symptom score of ≥2fortwourticaria symptoms for ≥3 days during the 7 days screening period and at randomization. The urticaria symptom score was based on the severity of pruritus, the number of wheals, and the maximumsizeofwhealswhichwereassesseddailyinthe morning and in the evening over the preceding 12 hour period (reflective) using 4 point scales of zero-three. The total symptom score was calculated as the sum of scores for pruritus, number of wheals, and wheal size.[15]

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.[11,16]

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.[12] 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 vitrodetection of specific IgE antibodies is a useful complementary tool for diagnosing type I allergy, particularly in people who are unable to undergo SPT.[17]

Histamine and Allergy

Several mediators are involved in the pathophysiology; however, histamine plays a vital role in the allergic immediate reaction [4]. Once an allergen is introduced to IgEsensitized mast cells, a degranulation is triggered which causes histamine to be released. The effects of histamines are mediated through several receptors including H1, H2, H3, and H4 receptors that belong to the superfamily of G-protein-coupled receptors [14]. The biological effects of histamine in the allergic reaction are mediated through

H1 receptors that coexist in active and inactive forms of g- protein-coupled receptors which balance each other. Histamine works as an agonist that pushes the balance to the active side leading to effects such as muscular contraction, bronchospasms, upregulation of endothelial permeability, and stimulation of sensory nerves and cough receptors [15]. H1 antihistamines work as inverse agonists that drive the balance toward the inactive side and suppress the effects of histamine. Since these effects are not genuine antagonistic but rather represent a balance displacement between active and inactive forms of H1 receptors, now, the term H1 antihistamine rather than the former “antihistamine antagonist” is used.[16]

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.[17]

Antihistamine[AH], e.g., **Bilastine** 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.[18]

Leukotriene Receptor Antagonist

The other major therapeutic class of drug as an add-on to antihistamine in the management of moderate severe AR are the LTRAs, e.g., **Montelukast**. LTRAs inhibit the activity of cysteinylleukotrienes (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 quality of life 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.[19,20]

Discussion

Clinical studies sponsored by the manufacturer of the drug have shown that bilastine 20 mg once daily is as effective as other non-sedating antihistamines for the treatment of seasonal allergic rhinoconjunctivitis and chronic idiopathic urticaria in children and adults from 12 and 18 years of age, respectively. Considering recent observations indicating that clinical trials sponsored by manufacturers more often than non-pharmaceutical company sponsored trials have favourable efficacy results it may be argued that further evaluations may be needed [12]. Certainly, the argument may be strengthened when part of the evidence is based on duplicate publications and post hoc analyses [16, 18, 19]. Further evidence testing is needed in patients with perennial rhino conjunctivitis in whom the only available study so far failed to prove any effect on the primary efficacy outcome measure. Such evaluations should be conducted during short-term (weeks) as well as during intermediate-term (6–12 months) treatment. Having said that,there may be no reasonto suspect that bilastine would not beas effective so thern on-sedating antihistamines in perennial rhinoconjunctivitis [1, 2]. That is probably why bilastine has received registration also for perennial rhinoconjunctivitis despite the fact that in that specific group of patients the evidence has been based on post hoc secondary efficacy outcome measures [15]. Finally, the observation that bilastine was efficacious in nasal obstruction supports other recent findings that oral and intranasal non- sedating anti-H1 antihistamines, as opposed to what was previously thought, indeed, are helpful in patients in whom nasal obstruction is a major concern [10]. International guidelines may need to be revised in the light of this evidence

Conclusions

Bilastine20mgoncedailyisaseffica ciousasother non-sedating antihistamines in allergic rhinoconjunctivitis and chronic urticaria. Bilastine is efficacious in all nasal symptoms including obstruction and in eye symptoms in patients with allergic rhinoconjunctivitis. Bilastine is well tolerated. In the fasting state bilastine is quickly absorbed, but the absorption is slowed when it is taken with food or fruit juice. Therefore, it is recommended that bilastine is taken at least one hour before and no sooner than two hours after a meal. International guidelines need to be revised in the light of the evidence of antihistamine effects on nasal obstruction. Research into pharmacokinetics, efficacy, and adverse effect profiles of bilastine in children under 12 years of age is needed as are dose-response assessments and studies planned rigorously with the aim of assessing quality of life effects

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