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Leukotriene Receptor Antagonist in Treating Allergic Rhinitis; Literature Review

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Abstract

A type 1 hypersensitivity disorder is Allergic rhinitis that affects the nasal mucosa and is described by frequent attacks of rhinorrhea and sneezing, nasal pruritus, and nasal congestion. It is the most regular disease stated in the ENT clinic and is generally controlled by nasal corticosteroids, vasoconstrictors, oral antihistamines, oral leukotriene receptor antagonists, or a medley of these agents. This study aimed to study the literature on the disease and to evaluate the effectiveness and safeness of leukotriene receptor antagonists compared with other therapeutic agents. We checked the PubMed database and searched for related articles toward the issue. We used the following Mesh words: Leukotriene receptor antagonists, rhinitis, allergic rhinitis, montelukast. The leukotriene (montelukast) receptor antagonist appears to play a restorative role in the treatment of patients with asthma and allergic rhinitis. However, compared with other agents, most current trials reported that montelukast provides greater effect in allergic rhinitis patients than placebo, especially nighttime symptoms, equal effect to antihistamine, and inferior to nasal corticosteroids. Additionally, montelukast, when combined with other agents, seems to provide a greater beneficial effect than monotherapy.

Keywords: Leukotriene receptor antagonist, Montelukast, Rhinitis, Allergic rhinitis, Anti-histamine, Nasal corticosteroids

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Introduction

The Joint Task Force Rhinitis Practice Parameter defines Rhinitis by one or more symptoms of the following: itching, sneezing, congestion, rhinorrhea (anterior and posterior), and usually with ocular symptoms, e.g. Itching, redness, puffy eyelids, and tears (Çobanoğlu *et al*., 2013; Settipane & Schwindt, 2013). Rhinitis is categorized as allergic or non-allergic, the latter being a diverse syndrome. Allergic rhinitis (AR) is classified as seasonal (commonly known as hay fever) as a result of internal allergens including animal dander and/or dust mites. Alternating; Or occupational (Settipane & Schwindt, 2013). AR is a type 1 hypersensitivity that affects the nasal mucosa and is identified by serial seizures attack, nasal congestion, an itchy nose, and rhinorrhea. In addition, AR is generally stimulated by putative antigens inhalation and mediated by immunoglobulin E (IgE) (Okubo *et al*., 2017).

It is noteworthy that AR patients also suffer from palate itching, post-nasal drainage, and pharynx. In addition, AR usually presents with painful comorbidities, such as sinusitis, nasal polyposis, asthma, respiratory tract infections, and otitis media (Çobanoğlu *et al*., 2013; Settipane & Schwindt, 2013). However the upper and lower airways have similar immunological, pathological, anatomical, and functional attributes, some AR clinical manifestations, e.g. pharyngolaryngeal symptoms overlap with asthma demonstrations (Imoto *et al*., 2019). The most regular atopic condition noticed in clinics of ENT is AR and international health problems in general trials. Medications, patient education, immunotherapy for allergens, control measures, and environmental are the foundation and basis of AR treatment, that enormously lessen the burden of disease. Rhinoplasty can be conducted as an adjunct therapy in chosen patients (Çobanoğlu *et al*., 2013). The majority of allergic rhinitis is increasingly influencing the world's population, affecting approximately 10 to 40 percent (Imoto *et al*., 2019), 39.4 percent of grown-ups in Japan while in the U.S the rate reaches 10 to 30 percent of the adult population (Okubo *et al*., 2017).

In addition, combined rhinitis (mixed allergic and non-allergic rhinitis) affects approximately 44 to 87% of AR patients and is more regular than non-allergic rhinitis or pure allergic rhinitis. The harshness and time of AR symptoms have been a significant burden on life quality of patients, activity, work productivity, and sleep (Settipane & Schwindt, 2013). In the year 2007 in a forthcoming cross-sectional survey, AR-related symptoms had a notable effect on the job or school activities in 74% of patients, sleep routines changed in about 50% of patients, while 61% of patients felt tired. 38. ٪ reported feeling irritability and 23.5 ٪ reported a general weakness (Kakli & Riley, 2016). AR risk elements are serum IgE above 100 IU / mL before age six, a positive allergy skin test, a family history of atopy, and higher socioeconomic status (Settipane & Schwindt, 2013). AR and its associated diseases lead to significant costs, direct (medical costs) and indirect (due to decreased work productivity and frequent sick leave). AR is also evaluated to be the fifth most expensive chronic disease in the U.S. (Settipane & Schwindt, 2013).

AR is usually diagnosed based on common allergy manifestation, where two or more of the classic AR symptoms may be sneezing, itching, and nasal congestion for more than an hour most days (Kakli & Riley, 2016). A physician should try to identify the allergic stimulus with a history. Family history of the atopic disease and typical allergens must be considered, which raises the likelihood of diagnosing AR. Some medicines, such as antihypertensives, local nasal decongestants, nonsteroidal anti-inflammatory drugs (NSAIDs), and aspirin, can stimulate or exacerbate present symptoms of AR. In addition, an assessment of past medical symptoms and history may be considered for the diagnosis of AR, e.g conjunctivitis, otitis media, asthma, and sleep disorders. People with AR usually do not differentiate the symptoms of AR from viral rhinitis (Kakli & Riley, 2016).

On the contrary, the physical review is important in AR diagnosis, which is helpful to rule out other diseases or even concomitant conditions. For instance, swelling of the nasal mucosa can result in dysfunction of the Eustachian tube, which develops shrinkage of the immobile tympanic membrane by pneumatic otoscopy. However, ear examinations are usually not significant in AR patients (Kakli & Riley, 2016). The American Academy of Otolaryngology-Head and Neck Surgery guidelines suggests allergy examination for the following conditions: 1) needs to identify the stimulated allergen for the target treatment or 2). The patient has a clinical diagnosis of AR but does not respond to experimental therapy. Allergy testing can be conducted as a skin examination or serum-specific IgE level (SSIge) (Kakli & Riley, 2016). The gold standard diagnostic examination is the pericardial skin test (SPT), which was used for over 100 years to diagnose atopic IgE-mediated diseases (Kakli & Riley, 2016).

Results and Discussion

Allergic Rhinitis Pathogenesis

Within minutes of allergen challenge, *initial phase response* appears by mast cell degranulation near the epithelium of the nasal mucosa following inhalation of airborne allergens e.g. animal dandruff, pollen, mold spores, and dust mites are seen in abundance (Nathan, 2003). As a result, histamine and other mediators, such as leukotriene and prostaglandin D2 (PGD2) are released, producing IgE antibodies from activated B lymphocytes, leading to bound allergen-specific IgE antibodies (Nathan, 2003; Okubo *et al*., 2017). The relations between allergen and IgE antibodies lead to the cross-linking of IgE molecules on the surface of mast cells, which create signals to the mast cells to be degranulated (release granules from cytoplasmic store). Thereby, pro-inflammatory mediators are produced, e.g. chemotactic agents (such as IL-5), cytokines, and histamine (e.g., tumor necrosis factor-α, interleukin [IL] -4) (Nathan, 2003). In addition, allergens cultivated mast cells and synthesized and released new inflammatory mediators including bradykinin, platelet-activating factors, leukotrienes, and prostaglandins. However, leukotrienes and histamine are thought to be necessary mediators in AR (Nathan, 2003).

Except for leukotriene, these intermediaries generate symptoms of nasal itching, sneezing, and rhinorrhea. In contrast, leukotriene release increases nasal airway resistance and vascular permeability, leading to nasal obstruction (Çobanoğlu *et al*., 2013; Okubo *et al*., 2017). Thus, AR is nowadays treated with leukotriene receptor antagonists (LTRA), steroids, vasoconstrictors, and antihistamines. Yet, intermediate to extreme patients who do not respond adequately to a monotherapy need mixed treatment. In these cases, mixed treatment is associated with decreased compliance and consequently lower life quality, and can also indicate a secondary economic burden on drug costs (Okubo *et al*., 2017).

The final phase reaction started when chemotactic factors were released by mast cells, which sustained the inflammatory reaction by encouraging the basophils migration, neutrophils, eosinophils, and T lymphocytes to the allergen site. These cells are accountable for the sustained response of the final stage, which begins hours after the allergen challenge., characterized by nasal obstruction in addition to the persistent early-phase symptoms (sneezing and rhinorrhea). In addition, cytokines e.g. IL-4, IL-5, IL-13, and cysteinyl leukotrienes released from white blood cells play an important role in proinflammatory intermediates for persistent inflammation and nasal symptoms, especially nasal congestion (Nathan, 2003). **Figure 1** demonstrate a summary of the early and late phase (Rahim *et al*., 2021).

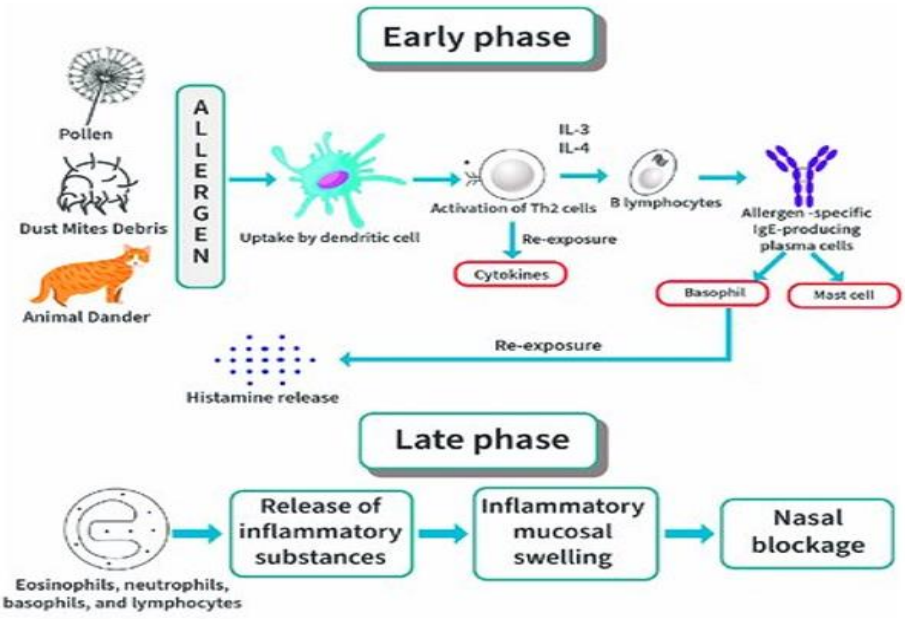

Figure 1. Pathophysiology of Early and Late Phase Allergic Rhinitis.

Leukotriene Receptor Antagonist

Normal Physiology, Mechanism of Action, and Adverse Effects

Leukotrienes (LTs) are inflammatory intermediates that operate in the natural defense of the host and are involved in inflammatory conditions. It is a derivative of arachidonic acid that is catalyzed by 5-lipoxygenase in two steps. LTs are involved in many provocative disorders, including asthma, AR, interstitial lung disease, chronic obstructive pulmonary disease (COPD), and obstructive bronchiolitis after lung transplantation. In addition, it is categorized into two classes: Cysteinyl LTs (CysLTs) and chemical adsorbent LTB4, which carry amino acids and fractions. BLT1 receptor and The LTB4 receptor are binds, which is one of the strongest chemicals for many immune cells. Investigations stated that BLT1 expression through non-myeloid cells e.g. skeletal muscle cells, nerve stem cells, endothelial cells, and vascular smooth muscle cells. Additional studies also documented that the LTB4-BLT1 axis is involved in a diversity of diseases other than allergic disorders, e.g. age-related macular degeneration, arthritis, cardiovascular disease, metabolic diseases, COPD, and cancer. While the BLT2 receptor is in the vicinity of BLT1 in humans and mice (Jo-Watanabe i., 2019).

Concerning CysLTs, investigations have indicated that they improve vascular permeability, guiding to nasal congestion, improved mucus production and secretion, rhinorrhea, and the uptake of inflammatory cells into tissues. Additional investigations also recommended the association of CysLTs in AR pathophysiology. Significantly, an enhance in the number of investigations has revealed that patients with AR respond favorably to develop CysLTs receptor antagonists of AR, e.g montelukast (MNT), zafirlukast, and pranlukast, which stop the impacts of CysLTs and advance the chronic respiratory diseases symptoms, especially AR and bronchial asthma (Jo-Watanabe *et al*., 2019).

Leukotriene antagonists operate by stopping the activity of leukotriene via two main mechanisms: 1) blockade of CysLT-1 receptors on target cells (such as Montelukast, Pranlocast, and Saffronlocast) or 2) inhibiting leukotriene synthesis by stopping the 5-lipoxygenase pathway (e.g., zileuton). While LTRAs are now known to play a role in the treatment of asthma, there is a growing interest in their results on AR. MNT is documented in the U.S only for seasonal allergic rhinitis treatment. to our knowledge, other LTRAs are not presently confirmed for allergic rhinitis but they have been investigated clinically and non-clinically for their effect on AR (Van Hoecke *et al*., 2007).

In addition, LTRAs are excreted through the biliary system, rapidly absorbed through the mouth, bind to approximately plasma proteins, and hepatic biotransformation. In general, LTRAs are well tolerated with few reported negative results, e.g. sneezing/fatigue, headache (5%), angioedema, pulmonary eosinophilia, rashes, dry mouth, upper respiratory tract infection, abdominal pain, dizziness, pruritus, sinusitis, arthralgia, and nasopharyngitis (Nayak & Langdon, 2007; Van Hoecke *et al*., 2007). Nevertheless, MNT has been stated to cause painless multiple ecchymotic lesions of 3-5 cm in the lower extremities of a 31-year-old woman known to have moderate persistent asthma, and AR (Aypak *et al*., 2013). Also, early concerns were attributed to the development of LTRAs-induced Strauss-Cherg syndrome in patients with asthma.

Nevertheless, the development of this syndrome was found to be attributed to corticosteroids withdrawal, indicating that LTRAs unmasked a pre-existing Churg-Strauss syndrome (Van Hoecke *et al*., 2007). MNT, the commonly used and only approved LTRAs, have been thoroughly studied and prescribed in asthma since the

late 1990s following multiple large, randomized, controlled clinical trials (Nayak & Langdon, 2007). It has a half-life of five hours and is administered once daily. Further, the recommended dose in adults is 10mg, 5mg in children from 6-14 years, and 4mg between 2 to 5 years of age (Van Hoecke *et al*., 2007).

Evidence-Based Medicine

Chen *et al*. had conducted an RCT on 46 participants, assessing the efficacy of MNT in addition to nasal budesonide (CD) compared to BD alone. Both regimens significantly improved the five main AR symptoms; however, the combination therapy provides superior efficacy than BD alone in nasal blockage, itching, and subclinical lower airway inflammation (Chen *et al*., 2021). Moreover, a single-center, randomized, open-label study comparing the efficacy of MNT and half-dose nasal BD combination to MNT or BD alone was conducted for 100 AR patients. The study resulted in significantly greater nasal congestion improvements than BD or MNT alone (Chen *et al*., 2018). Another RCT by Yamamoto *et al*. had examined the prophylactic efficacy of adding loratadine (antihistamine) to MNT compared to MNT alone. Similarly, the combination therapy provided a significant reduction in total scores of nasal symptoms ($P<0.05$), sneezing ($P<0.05$), and rhinorrhea ($P<0.05$) when compared to placebo addition to MNT (Yamamoto *et al.*, 2012). Also, Hung *et al*. had measured the exhaled nitric oxide (eNO) in children with perennial AR in response to four regimens; loratadine, loratadine with nasal cromoglycate, loratadine with oral MNT, and loratadine with nasal BD. The eNO, a simple and non-invasive method for assessing inflammatory airway disease, was successfully reduced in the nasal BD and MNT groups. Notably, children with perennial AR with high eNO levels might require oral MNT or nasal BD to prevent airway hyperresponsiveness (Hung *et al*., 2007).

In addition, a systematic review of seven investigations, such as 6,231 grown-ups with AR, evaluated the effectiveness of oral MNT monotherapy compared to MNT compounds. As a result, oral MNT extremely decreased, nocturnal nasal symptoms, quality of life compared with placebo, ocular symptoms, and daytime nasal symptoms. However, there was no considerable dissimilarity in oral antihistamine compared with oral MNT on nasal symptoms, eyesight, and life quality. In addition, MNT was lower in reducing nasal symptoms day and night compared to nasal BD. The mixture of antihistamines and MNT also provided more relief from ocular symptoms than antihistamines alone. Finally, nasal BD particularly reduced nasal congestion compared to the combination of MNT and antihistamines (Rodrigo & Yañez, 2006). According to the Rhinitis Severity Score (RSS), MNT, azelastine, and BD were compared in AR patients using RSS. Compared to placebo all three drugs were effective, but MNT was the most influential of the three drugs in relieving palate itching, throat, and ocular itching (Sardana *et al.*, 2010). Further, a systematic review and meta-analyses were conducted by Wilson *et al*., evaluating the efficacy of oral MNT compared with antihistamine and nasal BD. 11 studies were selected and showed that MNT is effectively better than placebo, a similar effect to antihistamines, but less effective than nasal BD in improving nasal, rhinoconjunctivitis and quality of life for AR patients (Wilson *et al*., 2004).

Liu *et al*. had conducted a meta-analysis comparing oral LTRA alone with combined LRTA with an antihistamine. Likewise, the combination therapy increased the therapeutic efficacy against daytime and composite nasal symptoms, including rhinorrhea, sneezing, and itching; nonetheless, it does not affect nighttime nasal symptoms and eye symptoms (Liu *et al*., 2018). Feng *et al*. conducted another meta-analysis and assessed the efficacy of oral LTRA compared with an oral antihistamine. While the 2 treatments are secure and influential in enhancing the AR patient's life quality, LTRA is better influential in enhancing nocturnal symptoms but less sufficient in enhancing during the day symptoms compare to antihistamines (Feng *et al*., 2021). Likewise, among nine studies with 5781 AR participants, Xu *et al.* had conducted a meta-analysis evaluating the safety and efficacy of selective antihistamine vs. LTRA. The meta-analysis showed that LTRA provides a greater effect for nighttime symptoms (difficulty going to sleep, nighttime awakening, and nasal congestion on awakening), the selective antihistamine is more effective for daytime nasal symptoms (congestion, rhinorrhea, pruritis, and sneezing) (Liu *et al*., 2016).

In addition, recent instruction suggests the use of LTRA in patients with AR and asthma, as it enhances both illnesses, however, this first-line treatment is not for independent AR. The FDA authorized LTRA (montelukast) for the treatment of seasonal AR in grown-ups and patients with children over two years of age and permanent AR in grown-ups and children over six months of age (Seidman *et al*., 2015). Based on the 2017 Joint Task Force on Practice Parameters, Intranasal corticosteroids for primary treatment of seasonal AR in patients over 15 years of age are superior to LTRA. (Wallace *et al*., 2017).

Conclusion

Allergic rhinitis is one of the commonest disorders worldwide, with a significant burden on healthcare costs, the productivity of patients, and life quality. Leukotriene receptor antagonists are an effective agent in an asthmatic patient. However, current guidelines recommend its use when allergic rhinitis coexists with asthma due to its beneficial effect in both conditions. LTRA, when combined with an antihistamine or nasal corticosteroids, provides a more significant effect than LTRA monotherapy. Additionally, nasal corticosteroids appear to provide a greater beneficial effect in comparison to LTRAs. Hence, the beneficial use of LTRA in allergic rhinitis must outweigh the risks, including side effects and costs.

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