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Role of Leukotriene Antagonists and Antihistamines in the Treatment of Allergic Rhinitis

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Abstract Allergic rhinitis is the most common atopic disorder seen in ENT clinics. It is diagnosed by history, physical exam and objective testing. Patient education, environmental control measures, pharmacotherapy, and allergen-specific immunotherapy are the cornerstones of allergic rhinitis treatment and can significantly reduce the burden of disease. Current treatment guidelines include antihistamines, intranasal corticosteroids, oral and intranasal decongestants, intranasal anticholinergics, intranasal cromolyn, and leukotriene receptor antagonists. In the mechanism of allergic rhinitis, histamine is responsible for major allergic rhinitis symptoms such as rhinorrhea, nasal itching and sneezing. Its effect on nasal congestion is less evident. In contrast, leukotrienes result in increase in nasal airway resistance and vascular permeability. Antihistamines and leukotriene receptor antagonists are commonly used in the treatment of allergic rhinitis. The published literature about combined antihistamines and leukotriene antagonists in mono- or combination therapy is reviewed and presented.

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Introduction

Recognised as one of the most common global health issue in general practice, allergic rhinitis (AR) affects at least 10–25 % of the world's population [1, 2]. Allergic rhinitis presents with nasal symptoms (concestion, rhinorhea, itching, sneezing) and is usually associated with ocular symptoms such as redness, puffy lids, tears, and itching. Patients suffering from allergic rhinitis also experience itching of the palate and pharynx and post-nasal drainage [3]. They also note significant effects on their quality of life. Furthermore, allergic rhinitis has some serious co-morbidities such as asthma, sinusitis, nasal polyposis, otitis media, and respiratory infections [4, 5].

Patient education, environmental control measures, pharmacotherapy, and allergen-specific immunotherapy are the cornerstones of allergic rhinitis treatment and can significantly reduce the burden of disease. Nasal surgery may be carried out as an adjunctive treatment in selected patients [6, 7]. Current treatment guidelines include antihistamines, intranasal corticosteroids, oral and intranasal decongestants, intranasal anticholinergics, and intranasal cromolyn and leukotriene receptor antagonists [8]. Pathophysiology of AR on the cellular and neurological basis must be clearly understood for adequate management. Studies on nasal challange with allergen or pro-inflammatory mediators following an assessment of cells and mediators released during the course of inflammation enlightened us on the mechanism of AR [9]. In animal and human models

of AR, the sequence of events occurs in two phases, chronologically termed early and late phase reactions.

Sensitization and early phase reactions: begin within minutes of allergen exposure. The human upper airway mucosa contains antigen-presenting cells (APCs), closely related monocytes/macrophages, and dendritic cells (DCs). DCs reside in the para- and intercellular channels surrounding the basal epithelial cells. They are the most effective cells for inducing and regulating the primary immune response [10]. When an inhaled allergen encounters APCs in the airway walls, sensitization takes place. APCs recognize, take up, and process the antigen into short peptides that associate with major histocompatibility complex (MHC) Class II molecules. APCs also transform naive T helper cells to Th2 cells by means of cytokines such as IL-4 [11]. Th2 cells further produce cytokines, such as IL-4 and IL-13, which serve several functions, including promotion of antigen-specific IgE production by B cells. Specific B cell subsets transform into plasma cells, which switch from IgM to IgE production [12]. Memory B cells play an essential role in maintaining established antibody responses. IgE antibodies "sensitize" a group of cells including mast cells, which originate from bone marrow precursors expressing the CD34 molecule. Mast cells express a high-affinity receptor for the Fc region of IgE which binds irreversibly to the mast cells. Cross-linking of two or more IgE molecules on the mast cell occurs, clustering intracellular domains of the cell-bound Fc receptors, leading to a complex sequence of reactions which trigger degranulation of vesicles of mast cells. Subsequently, mast cells release a cascade of preformed and newly produced inflammatory mediators resulting in acute airway obstruction. Preformed mediators such as histamine and tryptase released from mast cells cause localized inflammation. This early phase involves degranulation of the mast cells and release of histamine, tryptase (mast cell-specific marker), kininogenase, heparin, and other enzymes. In addition, mast cells create some inflammatory mediators that are not preformed or stored, such as prostoglandin D2 and the sulfidopeptidyl leukotrienes LTC4, LTD4, and LTE4 [6]. These mediators cause blood vessel leakage, and produce mucosaledema and the watery rhinorrhea as characteristics of allergic rhinitis. Glands secrete mucoglycoconjugates and antimicrobial compounds and help dilate blood vessels to cause sinusoidal filling with resulting occlusion and congestion of nasal air passages. Mediators also stimulate sensory nerves to cause nasal itch and congestion; meanwhile, systemic reflexes such as sneezing occurs [6]. The above responses develop within minutes of allergen exposure and are termed the early phase, or "immediate," allergic response [13]. This early phase of allergic response in AR is manifested as sneezing, itching and watery discharge [14].

Late phase: the characteristics of late phase reaction include increased numbers of Th2 lymphocytes, eosinophils, basophils, and neutrophils, which release cytokines and other mediator molecules. Eosinophils produce superoxide anion and hydrogen peroxide that promote intense inflammatory reactions. Eosinophils also induce chemo-attractants such as interleukin-5 and eotaxin, and its granular products, such as major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin, play a role in inducing nasal hyper-reactivity. These proteins are capable of causing severe damage to airway epithelium and exposing local nerve fibers [15]. Mast cell mediators including prostaglandin D2 (PGD2), leukotriene C4, platelet-activating factor, cytokines, and eosinophil chemotactic factor help in sustaining inflammation by causing chemotaxis-specific attraction of neutrophils and eosinophils. Th2 lymphocytes secrete several cytokines such as IL-3, IL-4, IL-5, and IL-13. IL-4 and IL-13 are known to stimulate secretion of RANTES (regulated on activation of normal T cells expressed and secreted) eotaxin, membrane co-factor protein, and eosinophil chemotactic factor within fibroblasts. IgE receptor activation induces degradation of leukotrienes and prostaglandins.

Leukotrienes attract eosinophils, increase microvascular leakage, edema, and mucous gland secretion and enhance the kinin action [16]. Attachment, adhesion, and transendothelial migration of eosinophils to the site of inflammation are upregulated by Th2 cytokines by inducing expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin on the vascular endothelium [17]. TNF-α, generated from inflammatory cells in response to IL-4, may induce the expression of VCAM-1 that subsequently activates certain subsets of leukocytes resulting in both increased expression and prolonged appearance of VCAM-1 on the endothelium [18]. Symptomatically, late phase reaction is manifested by nasal congestion and nasobronchial hyper-reactivity [15].

The Role of Histamine and Antihistamines in Allergic Rhinitis

Histamine was defined in the 1920s as a major mediator in allergic disorders, but the mechanism remained unknown until histamine H1 receptor was identified in 1966 [19].

Histamine plays a pivotal role in allergic inflammation. It is released after the IgE-mediated activation of mast cells and basophils following allergen trigger in sensitized patients [9]. Nasal challenge with histamine causes sneezing, pain, pruritus, rhinorrhea, and nasal blockade [20]. Sensorial neurons activated by histamine causes sneezing and itching, in addition to activating a neuronal increase in nasal parasympathetic activity which stimulates nasal submucosal glands and increases invascular permeability, causing rhinorrhea [21]. Molecular studies have found that 4 histamine receptor subtypes (H1, H2, H3, and H4) occur in normal nasal mucosa studies with higher expression of H1 and H2 in atopic individuals [22]. Most of the effects of histamine in allergic disease are mediated through H1 receptors, but cutaneous itch and nasal congestion may involve both H1 and H3 receptors [23]. Histamine also activates the H2 receptors on the smooth muscle cells that surround nasal capacitance vessels which causes smooth muscle relaxation. Histamine is probably the most important mediator in the early phase reaction following an allergen nasal challenge but also plays a role in the late phase response [4]. H1-receptor activation has proinflammatory activity, and is involved in the development of several aspects of antigen-specific immune response, including the maturation of dendritic cells, and the modulation of the balance between type 1 helper (Th1) T cells, and type 2 helper (Th2) T cells. Histamine also induces the release of proinflammatory cytokines and lysosomal enzymes from human macrophages and has the capacity to influence the activity of basophils, eosinophils, and fibroblasts [23].

There are six chemical groups of antihistamines defined as ethanolamines, ethylendiamines, alkylamines, piperazines, piperidines, and phenothiazines. But antihistamines are usually classified according to their function and adverse effect profiles into first or second generation. There is also third generation antihistamines category [6]. First generation antihistamines (chlorpheniramine, clemastine, ketotifen, hydroxyzine, mequitazine) are widely available over-the-counter, effective and economical; however, their usefulness is limited by their potential to induce sedation due to significant capasity of crossing the blood–brain barrier in 10–40 % of users. Anticholinergic effects such as drying of mucous membranes, urinary retention, constipation, tachycardia, and blurred vision may preclude their use in elderly patients [12]. In general, first generation H1 antihistamines are rapidly metabolized and thus they must be administered three or four times a day [24].

Over the last 2 decades, pharmacological research produced second generation antihistamines which have higher potency, faster onset, and minimal sedative effects [25]. Terfenadine and astemizole were the earliest second-generation antihistamines with low CNS penetration. However, due to their potential for arrhythmia in susceptible individuals, these agents were withdrawn from the market. Loratadine and cetirizine are commonly used less-sedating antihistamines [12]. These agents have good efficacy and low propensity for several troublesome side effects, due to their low brain penetration [26]. Levocetirizine, an enantiomer of cetirizine, also has the potential to induce sedation at recommended doses. It also has better therapeutic index compared to cetrizine. Active metabolites or enantiomers of first or second generation antihistamines (levocetrizine, fexofenadine, desloratadine) are classified as third generation antihistamines [6]. Intranasal H1 antihistamines, such as azelastine and levocabastine, are also useful in mild-to-moderate allergic rhinitis [27]. These topical antihistamines are administered twice daily, and have a rapid onset of action. Both azelastine and levocabastine have been shown to improve symptoms in patients with seasonal or perennial allergic rhinitis; however, the bitter taste has been described as an adverse effect of azelastine [28]. Unlike oral antihistamines which have demonstrated reduction in nasal itch and rhinorrhea, but not universally demonstrated improvement in the symptom of nasal stuffiness, nasal agents have demonstrated reduction in this very bothersome symptom.

The Role of Leukotrienes (LTs) and Leukotriene Receptor Antagonists (LTRAs) in Allergic Rhinitis

Leukotrienes, described in the late 1970s, are a family of inflammatory lipid mediators that are arachidonic acid metabolites [29]. LTs are synthesized from arachidonic acid by the 5-lipoxigenase (5-LO) pathway. An unstable intermediate product, LTA4, is formed and converted successively to LTC4, LTD4, and LTE4. A separate pathway produces LTB4. LTC4 is metabolized enzymatically to LTD4 and subsequently to LTE4, which is excreted in the urine. Several cells such as mast cells, basophils, eosinophils, monocytes/macrophages, dendritic cells and T lymphocytes can produce leukotriens in response to receptor-activated, antigen–antibody interaction [30]. The 2 classes of leukotriens, LTB4 and peptidyl-cysteinyl leukotriens, also have important mediator functions in the upper airways. Because of the presence of amino acid in their structure, LTC4, LTD4, and LTE4 are collectively named cysteinyl leukotrienes (CysLTs). They promote inflammatory cell recruitment and activation (primarily of eosinophils) as well as fibrosis and airway remodeling, with actions such as smooth muscle cell and epithelial cell proliferation. The first step of eosinophil recruitment is increasing adherence to the vascular endothelium. The cysLTs increase expression of adhesion molecules such as P selectin. They also promote eosinophilia by reducing eosinophil apoptosis. The cysLTs may also promote

airway remodeling by increasing the deposition of collagen below the basement membrane, enhancing collagen synthesis and degradation by fibroblasts, and promoting the proliferation of bronchial epithelial cells and smooth muscle cells. LT modifiers can reduce cytokine expression by blocking their actions. The reverse is also true: cytokines can modulate LT expression [31]. During the early phase response to antigen, CysLTs are released by mast cells and basophils, while in late phase they are synthesized by eosinophils and macrophages [32]. CysLTs causes contraction of bronchial smooth muscles, mucous production, edema, and increased vascular permeability. LTD4 challenge in human causes an increase in nasal mucosal blood flow and airway resistance [33]. Antileukotriene drugs are classified into 2 groups, based upon their mechanism of action:

A) Cysteinyl leukotriene receptor antagonists work by blocking the leukotriene receptor and thus block the end organ response of leukotriene. This group includes zafirlukast, pranlukast, and montelukast
B) Leukotriene synthesis inhibitors (5-lipoxygenase inhibitor) work by blocking the biosynthesis of cysteinyl leukotrienes and LTB4. They include zileuton, ZD-2138, Bay X 1005, and MK-0591 [34].

Leukotriene receptor antagonists (LTRAs) have demonstrated efficacy in asthma. As there is a significant link between allergic rhinitis and asthma, with similar inflammatory mechanisms, it is not surprising that LTRAs have taken a role in the management of allergic rhinitis. They are characterized by a rapid oral absorption, a near total plasma protein binding, a hepatic biotransformation, and are principally excreted by the liver [9]. Among CysLT1 receptor antagonists, montelukast is the only drug approved for treatment of allergic rhinitis. Studies have shown that montelukast provides statistically significant improvements in nasal symptoms; however, topical corticosteroids and oral antihistamines provide a greater reduction in nasal symptom scores. It has been shown that montelukast reduces daytime congestion, rhinorrhea, pruritus, and sneezing. There is a greater treatment effect seen in patients with higher pollen levels. It also relieves the difficulty in sleeping. It reduces the number of peripheral blood eosinophils due to its anti-inflammatory effect [12]. The effect of montelukast in reducing nasal symptom scores appears to be additive with antihistamines [35]. Montelukast is considered to be a very safe drug for use in the prophylaxis and therapeutic treatment of airway allergy including in children. However, recent reports have demonstrated that there is a possibility of association of montelukast use with several adverse psychiatric events, such as agitation, aggression, anxiousness, hallucination, depression, and insomnia [36].

Combined Leukotriene Receptor Antagonists and Antihistamines

When one examines the pathophysiology of allergic rhinitis, histamine is responsible for many of the symptoms of allergic rhinitis, including rhinorrhea, nasal itching, and sneezing. Its effect on nasal congestion is less evident. In contrast, leukotriens mainly cause increases in nasal airways resistance and vascular permeability [37]. Antihistamines and LTRAs are frequently used in the treatment of allergic rhinitis. The blockage or inhibition of these two mediators may provide additional benefits compared to a single mediator inhibition [6]. There are a number of studies available based on this topic.

A double-blind, parallel group, placebo-controlled study was held in 60 seasonal allergic rhinitis patients, in which therapy was begun before the expected beginning of the grass pollen season. Group A: placebo for both cetrizine and montelukast; and group B: active montelukast plus placebo for cetrizine; group C: active cetrizine plus placebo for montelukast; and group D: active cetrizine plus active montelukast were given for 6 weeks of the pollen season. In this study, combined montelukast/cetrizine pretreatment significantly reduced the season symptom scores for sneezing, eye and nasal itching, rhinorrhea, and congestion [38].

In another multicentered double-blind, randomized, parallel group, placebo-controlled 2-week trial, 460 men and women with spring seasonal allergic rhinitis were randomly treated with one of the following regimens: montelukast 10 or 20 mg, loratadine 10 mg, montelukast 10 mg with loratadine 10 mg, or placebo. In this clinical trial, concomitant montelukast and loratadine provided the most effective treatment for seasonal allergic rhinitis and associated eye symptoms, with a safety profile compared with placebo [2].

In a 32-week randomized, double blind, placebo-controlled, crossover study with 40 patients, 20 patients received montelukast/desloratadine or placebo, and 20 patients received montelukast/levocetrizine and placebo. The treatment periods were separated by 2-week wash-out periods and it was concluded that combining montelukast with either levocetrizine or desloratadine gave additional benefits in comparison to each agent alone [39]

Not all studies have demonstrated added efficacy, however; in another study, that was carried with 115 children treated with montelukast and loratadine, there were no significant differences in the total daytime nasal symptom scores when compared to the individual components [40].

The onset of the action of loratadine/montelukast combination in ragweed-sensitive allergic rhinitis subjects was explored via environmental exposure unit study which demonstrated the onset of action was 1 h 15 min. That paper also concluded that loratadine combined with montelukast

reduced nasal congestion as indicated by significant improvements in nasal congestion scores, while the incidence of adverse events was similar between the groups [41].

A concomitant antihistamine/LTRA treatment compared with intranasal corticosteroid (fluticasone propionate) in a study demonstrated that fluticasone propionate was more effective than combined montelukast and loratadine or combined montelukast and cetrizine for the nasal inflammation and the control of nasal symptoms [42, 43].

Another systematic review of randomized controlled trials showed that, in improving nasal and eye symptoms and quality of life, LTRA and antihistamine is more effective than antihistamine alone, but inferior to intranasal corticosteroids for treating seasonal allergic rhinitis [44]. However, in another study, Lee at al. compared fexofenadyn (fex), montelukast (ml) and combined fexofenadyn montelukast (fex + ml) and showed that the combined therapy significantly attenuated the response to nasal AMP challenge and improved nasal symptoms compared with fexofenadyn or montelukast alone [45]

Allergic rhinitis and its treatment is also a significant economic burden. The cost and resource utilization comparisons of second generation antihistamines versus montelukast for allergic rhinitis treatment was evaluated in a study in 2009, and showed that newly diagnosed allergic rhinitis patients initially prescribed montelukast experience higher medical costs and utilization than patients prescribed other branded second generation antihistamines [46].

Finally, in general, there are advantages and disadvantages in using combined montelukast and loratadine/cetrizine treatments. They provide effective treatment for seasonal allergic rhinitis and associated eye symptoms with a safety profile compared with second generation antihistamines or placebo. Combination therapy seems to be a more effective strategy than monotherapy in the treatment of allergic rhinitis in patients with moderate to severe symptoms, although less effective than nasal corticosteroids. Prescribing only one concomitant tablet makes patient compliance better. Adverse effects are nearly the same as taking antihistamines. It can be used effectively in patients that have contradictions using intranasal corticosteroids. Despite these advantages, recent studies have demonstrated that combined LTRA/AH treatment was not superior to intranasal corticosteroids in the treatment of seasonal allergic rhinitis. Although data exist indicating that nasal corticosteroids may be more effective than combination therapy for some symptoms, combination therapy can still be a worthwhile choice in allergic rhinitis. First, adherence to a pill containing combination therapy is greater than compliance to nasal corticosteroids. In addition, despite the safety of nasal corticosteroids, some patients are still unwilling to use these medications in the long term. Recent advances in antileukotriene therapy show that early and late phases in allergic rhinitis are better controlled with combination therapy [47]. Likewise, there is a robust literature demonstrating that adherence with a pill is greater than that with. Above and beyond this, some patients are simply unwilling to use a nasal corticosteroid.

Conclusions

Combined LTRA/AH treatment not only constitutes a good therapeutic option in AR patients who do not tolerate or did not benefit from intranasal steroids, but administration of LTRA and AH in a single pharmaceutical form may also improve patient compliance.

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References

1. Valk PJ, Simons M. Effects of loratadine/montelukast on vigilance and alertness task performance in a simulated cabin environment. Adv Ther. 2009;26(1):89–98.
2. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA (2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8–160.
3. Meltzer EO, Malmstrom K, Lu S, Prenner BM, Wei LX, Weinstein SF, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol. 2000;105(5):917–22.
4. Cingi C, Kayabasoglu G, Nacar A. Update on the medical treatment of allergic rhinitis. Inflamm Allergy Drug Targets. 2009;8 (2):96–103.
5. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012;50(1):1–12.
6. Van Hoecke H, Vandenbulcke L, Van Cauwenberge P. Histamine and leukotriene receptor antagonism in the treatment of allergic rhinitis: an update. Drugs. 2007;67(18):2717–26.
7. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization position paper 2009. Allergy. 2009;64 Suppl 91:1–59.
8. Lagos JA, Marshall GD. Montelukast in the management of allergic rhinitis. Ther Clin Risk Manag. 2007;3(2):327–32.
9. Al Suleimani YM, Walker MJ. Allergic rhinitis and its pharmacology. Pharmacol Ther. 2007;114(3):233–60.
10. Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, et al. Immunobiology of dendritic cells. Annu Rev Immunol. 2000;18:767–811.
11. Lambrecht BN. Allergen uptake and presentation by dendritic cells. Curr Opin Allergy Clin Immunol. 2001;1(1):51–9.
12. Takhar P, Corrigan CJ, Smurthwaite L, O'Connor BJ, Durham SR, Lee TH, et al. Class switch recombination to IgE in the bronchial mucosa of atopic and nonatopic patients with asthma. J Allergy Clin Immunol. 2007;119(1):213–8.

13. Grønborg H, Bisgaard H, Rømeling F, Mygind N. Early and late nasal symptom response to allergen challenge. The effect of pretreatment with a glucocorticosteroid spray. Allergy. 1993;48 (2):87–93.
14. Min YG. The pathophysiology, diagnosis and treatment of allergic rhinitis. Allergy Asthma Immunol Res. 2010;2(2):65–76.
15. Mandhane SN, Shah JH, Thennati R. Allergic rhinitis: an update on disease, present treatments and future prospects. Int Immunopharmacol. 2011;11(11):1646–62.
16. Smith LJ. Pharmacology and safety of the leukotriene antagonists. Clin Rev Allergy Immunol. 1999;17(1–2):195–212.
17. Venarske D, de Shazo RD. Molecular mechanisms of allergic disease. South Med J. 2003;96(11):1049–54.
18. Iademarco MF, Barks JL, Dean DC. Regulation of vascular cell adhesion molecule-1 expression by IL-4 and TNF-alpha in cultured endothelial cells. J Clin Investig. 1995;95(1):264–71.
19. Taylor-Clark T, Foreman J. Histamine-mediated mechanisms in the human nasal airway. Curr Opin Pharmacol. 2005;5(3):214–20.
20. Doyle WJ, Boehm S, Skoner DP. Physiologic responses to intranasal dose-response challenges with histamine, methacholine, bradykinin, and prostaglandin in adult volunteers with and without nasal allergy. J Allergy Clin Immunol. 1990;86(6 Pt 1):924–35.
21. Baroody FM, Naclerio RM. Antiallergic effects of H1-receptor antagonists. Allergy. 2000;55(64):17–27.
22. Nakaya M, Takeuchi N, Kondo K. Immunohistochemical localization of histamine receptor subtypes in human inferior turbinates. Ann Otol Rhinol Laryngol. 2004;113(7):552–7.
23. Akdis CA, Blaser K. Histamine in the immune regulation of allergic inflammation. J Allergy Clin Immunol. 2003;112 (1):15–22.
24. Camelo-Nunes IC. Newantihistamines: a critical view. J Pediatr (Rio J). 2006;82(5):S173–80.
25. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126(3):466–76.
26. Cingi C, Gunhan K, Gage-White L, Unlu H. Efficacy of leukotriene antagonists as concomitant therapy in allergic rhinitis. Laryngoscope. 2010;120(9):1718–23.
27. Lee C, Corren J. Review of azelastine nasal spray in the treatment of allergic and non-allergic rhinitis. Expert Opin Pharmacother. 2007;8(5):701–9.
28. Canonica GW, Ciprandi G, Petzold U, Kolb C, Ellers-Lenz B, Hermann R. Topicalazelastine in perennial allergic conjunctivitis. Curr Med Res Opin. 2003;19(4):321–9.
29. Murphy RC, Hammarström S, Samuelsson B. Leukotriene C: a slow-reacting substance from murine mastocytoma cells. Proc Natl Acad Sci U S A. 1979;76(9):4275–9.
30. Peters-Golden M, Gleason MM, Togias A. Cysteinylleukotrienes: multi-functional mediators in allergic rhinitis. Clin Exp Allergy. 2006;36(6):689–703.
31. Haberal I, Corey JP. The role of leukotrienes in nasal allergy. Otolaryngol Head Neck Surg. 2003;129(3):274–9.
32. Peters-Golden M, Henderson Jr WR. The role of leukotrienes in allergic rhinitis. Ann Allergy Asthma Immunol. 2005;94 (6):609–18.
33. Busse W, Kraft M. Cysteinyl leukotrienes in allergic inflammation: strategic target for therapy. Chest. 2005;127(4):1312–26.
34. Elnabtity MH, Singh RF, Ansong MA, Craig TJ. Leukotriene modifiers in the management of asthma. J Am Osteopath Assoc. 1999;99(7):S1–6.
35. Nayak A, Langdon RB. Montelukast in the treatment of allergic rhinitis: an evidence-based review. Drugs. 2007;67(6):887–901.
36. Grainger J, Drake-Lee A. Montelukast in allergic rhinitis: a systematic review and meta-analysis. Clin Otolaryngol. 2006;31 (5):360–7.
37. Samaria JK. Anti leukotriene drugs: are they really useful? J Indian Acad Clin Med. 2000;5(1):41–4.
38. Kurowski M, Kuna P, Górski P. Montelukastpluscetirizine in the prophylactic treatment of seasonal allergic rhinitis: influence on clinical symptoms and nasal allergic inflammation. Allergy. 2004;59(3):280–8.
39. Ciebiada M, Ciebiada MG, Kmiecik T, DuBuske LM, Gorski P. Quality of life in patients with persistent allergic rhinitis treated with montelukast alone or in combination with levocetirizine or desloratadine. J Investig Allergol Clin Immunol. 2008;18(5):343–9.
40. Watanasomsiri A, Poachanukoon O, Vichyanond P. Efficacy of montelukast and loratadine as treatment for allergic rhinitis in children. Asian Pac J Allergy Immunol. 2008;26(2–3):89–95.
41. Day JH, Briscoe MP, Ratz JD, Ellis AK, Yao R, Danzig M. Onset of action of loratadine/montelukast in seasonal allergic rhinitis subjects exposed to ragweed pollen in the Environmental Exposure Unit. Allergy Asthma Proc. 2009;30(3):270–6.
42. Pullerits T, Praks L, Ristioja V, Lötvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 2002;109(6):949–55.
43. Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasonepluscetirizine, fluticasoneplus montelukast and cetirizineplus montelukast for seasonal allergic rhinitis. Clin Exp Allergy. 2004;34(2):259–67.
44. Rodrigo GJ, Yañez A. The role of anti leukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. Ann Allergy Asthma Immunol. 2006;96(6):779–86.
45. Lee DK, Jackson CM, Soutar PC, Fardon TC, Lipworth BJ. Effects of single or combined histamine H1-receptor and leukotriene CysLT1-receptor antagonism on nasal adenosine monophosphate challenge in persistent allergic rhinitis. Br J Clin Pharmacol. 2004;57(6):714–9.
46. Hay J, Jhaveri M, Tangirala M, Kaliner M. Cost and resource utilization comparisons of second-generation antihistamines vs. montelukast for allergic rhinitis treatment. Allergy Asthma Proc. 2009;30(6):634–42.
47. Scadding GW, Scadding GK. Recent advances in antileukotriene therapy. Curr Opin Allergy Clin Immunol. 2010;10(4):370–6.