

## Review Article

# Anti-Leukotrienes in the treatment of allergic conjunctivitis and comorbidities in children: An update

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**Abstract.** The term “Allergy” actually includes a variety of different diseases (rhinitis, conjunctivitis, asthma, urticaria, and dermatitis) with a common pathological basis linked to the release of chemical mediators such as histamine, platelet-activating factor, arachidonic acid metabolites, and chemotactic factors secreted by mastocytes, basophils, and eosinophils. The key-role of leukotrienes (LTs) as mediators in allergic and inflammatory response justifies possible therapeutic use of leukotriene antagonists in other allergic diseases beyond asthma. LTs modifiers reduce asthma symptoms, short-acting beta2-antagonist (SABA) use, and asthma exacerbations, and improve all indexes of pulmonary function, as measured by the increases in forced expiratory flow at one second (FEV1), peak expiratory flow (PEF), quality of life, and indices of bronchial inflammation (blood eosinophils, inflammatory cells in the bronchial mucosa, exhaled nitric oxide, substance P, neurokinin A, eosinophil cationic protein, and serum myeloperoxidase). Anti-LTs have also been successfully used by some authors to control allergic diseases such as rhinitis, atopic dermatitis, chronic urticaria and allergic conjunctivitis. Moreover, recently, new reports have been published concerning other conditions (migraine prophylaxis, sleep disorders, inflammatory bowel disease, and nasal polyposis) that broaden the future range of clinical applications. Topical ocular montelukast can be a potential therapeutic drug with a new route of administration that can be used for treatment of allergic conjunctivitis.

**Keywords:** Antileukotriene drugs, children, atopic diseases

## 1. Introduction

The term “Allergy” includes a variety of different illnesses (rhinitis, conjunctivitis, asthma, urticaria, and dermatitis) with a common pathological basis [1], linked to the release of chemical mediators such as histamine, platelet-activating factor, metabolites of arachidonic acid, and chemotactic factors from mas-

tocytes, basophils, and eosinophils. The key role of leukotrienes (LTs) as mediators in allergic and inflammatory response justifies the new pharmacologic category of Cysteinil LT antagonists as possible therapeutic use in other allergic diseases beyond asthma.

Since 1938, known as slow-reacting substances of anaphylaxis [2], even if LTs are known as products of the arachidonic acid metabolism pathway by the action of 5-lipoxygenase only in the last seventies. LTs are generated by a number of cells including mast cells, eosinophils, basophils, and neutrophils, sited in

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Table 1.  
Uses of Anti-leukotrienes drugs for other diseases beyond asthma as described in literature

| Pathologies in which TRAs Have been successfully used | References of the literature                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sinonasal polyposis                                   | – Kieff DA, Busaba NY. Efficacy of Montelukast in the treatment of nasal polyposis. <i>Ann Otol Rhinol Laryngol</i> 2005; 114(12): 941-5.<br>– Mostafa BE, Abdel Hay H, Mohammed HE, Yamani M. Role of leukotriene inhibitors in the postoperative management of nasal polyposis. <i>ORL J Otorhinolaryngol Relat Spec.</i> 2005; 67(3): 148-53.                                                                                                |
| Sleep breathing disorders                             | – Kheirandish L, Goldbart AD, Gozal D. Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. <i>Pediatrics</i> 2006; 117(1): e61-6.<br>– Goldbart AD, Goldman JL, Veling MC, Gozal D. Leukotriene modifier therapy for mild sleep-disordered breathing in children. <i>Am J Respir Crit Care Med</i> 2005 Aug 1; 172(3): 364-70. Epub 2005 May 5. |
| Migraines                                             | – Sheftell F, Rapoport A, Weeks R, Walker B, Gammerman I, Baskin S. Montelukast in the prophylaxis of migraine: a potential role for leukotriene modifiers. <i>Headache</i> 2000; 40(2): 158-63.                                                                                                                                                                                                                                                |
| Esophagitis                                           | – Attwood SE, Lewis CJ, Bronder CS, Morris CD, Armstrong GR, Whittam J. Eosinophilic esophagitis: a novel treatment using Montelukast. <i>Gut</i> . 2003; 52(2): 181-5.                                                                                                                                                                                                                                                                         |
| Eosinophilic gastroenteritis                          | – Daikh BE, Ryan CK, Schwartz RH. Montelukast reduces peripheral blood eosinophilia but not tissue eosinophilia or symptoms in a patient with eosinophilic gastroenteritis and esophageal stricture. <i>Ann Allergy Asthma Immunol</i> 2003; 90(1): 23-7.                                                                                                                                                                                       |
| Inflammatory bowel disease                            | – Vanderhoof JA, Young RJ, Hanner TL, Kettlehut B. Montelukast: use in pediatric patients with eosinophilic gastro intestinal disease. <i>J Pediatr Gastroenterol Nutr</i> 2003; 36(2): 293-4.<br>– Friesen CA, Kearns GL, Andre L, Neustrom M, Roberts CC, Abdel-Rahman SM. Clinical efficacy and pharmacokinetics of montelukast in dyspeptic children with duodenal eosinophilia. <i>J Pediatr Gastroenterol Nutr</i> 2004; 38(3): 343-51.   |

the airways of patients with asthma and in the skin of patients with chronic urticaria (CU). They mediate chemotaxis, vascular permeability, edema, eosinophils migration, airway constriction, and smooth muscle contraction [3].

As they present a long time efficacy, these molecules are defined as “slow reacting substances”. Among LTs, LTB<sub>4</sub>, LTC<sub>4</sub>, and LTD<sub>4</sub> have particularly potent effects. LTB<sub>4</sub> is a leukocyte chemoattractant and is involved in the migration of granulocytes into tissues [4,5]. LTC<sub>4</sub> evokes a wheal and flare reaction when intradermally injected. LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> are chemical mediators of the inflammation involved in the pathogenesis of asthma, the overall biological effects of which are bronchial constriction and an increase in both mucus secretion and vascular permeability [6–14].

Recent studies performed on adult patients suggest that anti-LTs can play an important role not only in the acute phase but also in controlling the chronic development of bronchial asthma. Moreover, anti-LTs have successfully been used by some authors to control allergic diseases such as rhinitis, atopic dermatitis, chronic urticaria and allergic conjunctivitis. In addition, new reports have been published concerning the use of anti-LTs in other conditions (migraine prophylaxis, sleep disorders, inflammatory bowel disease,

and nasal polyposis) prospecting a wider range of clinical applications (Table 1).

## 2. Recent applications of antileukotrienes drugs beyond asthma

### 2.1. Paranasal sinus disease

LTs are inflammatory mediators that have an important role in paranasal sinus disease (PSD) and the formation of nasal polyps (NP) [15]. Cys-LTs are overproduced in asthmatic subjects with chronic hyperplastic rhinosinusitis (CHR) and NP [16]. In view of the fact that these agents lead to symptoms in asthmatic patients, the use of LTRAs, particularly montelukast and zafirlukast, seems appropriate [17, 18]. In addition, it has been suggested that many aspirin-intolerant asthma patients have NP and that treatment with the LTRAs results in improvement and resolution of the NP [19–21]. The LTRAs might be good alternatives to the long-term administration of oral steroids, in view of their systemic anti-inflammatory effects and acceptable safety profiles [22–25].

## 2.2. Migraine

Migraine (M) is a paroxysmal disorder characterized by recurrent attacks of headache, without associated visual and gastrointestinal disturbances. M can be classified in two main groups: Common and classic. There is evidence that confirms the important roles of AA, prostaglandins, and LTs in the pathogenesis of M, based on measurements of these substances in biological fluids during and after the attack [26,27]. Non-steroidal anti-inflammatory agents (NSAIDs) have been widely used for treating Migraine [28]. The pathogenesis of M is not well understood and there is need for prophylactic medications. Inhibition of mast cells release of anti-LT and other vasoactive molecules may be such an approach [29,30].

## 2.3. Chronic urticaria

Although an autoimmune/autoreactive basis probably underlies most cases of chronic urticaria auto-antibodies to the high affinity IgE receptor [31,32] can be detected in about 35% of patients with chronic urticaria, whereas in about 5–10% of patients anti-IgE auto-antibodies can be found. In these cases it is difficult to define the efficacy of LTRAs as therapy of these forms.

However several studies seem to demonstrate that combined therapy with montelukast and zafirlukast produced significantly greater improvement than placebo or cetirizine mono-therapy [33–36].

## 2.4. Atopic dermatitis

Atopic dermatitis (AD) is a chronic, relapsing, eczematous disorder of the skin that occurs in patients of all ages, but is more common in children. AD is associated with other atopic diseases such as allergic rhino-conjunctivitis and bronchial asthma [37]. Nearly 80% of children with AD eventually develop allergic rhinitis or asthma. AD is classified as mixed (i.e., cases associated with respiratory allergies) or pure, with intrinsic and extrinsic variants [38]. In the extrinsic type, interleukin-4 (IL-4) is secreted by T-cells isolated from spontaneous lesions and skin-derived T lymphocytes express more IL-13 [39]. There is evidence for enhanced LTs production in the pathogenesis of AD [40]. It has been suggested that LTRAs may be more successful for the treatment of the extrinsic subgroup of AD and to be a safe and

effective alternative to steroid-sparing therapy in the management of patients with AD [41–43]. The same was true in pediatric patients treated with chewable montelukast day (5 mg/day for 24 wk) [44].

## 2.5. Bronchiolitis

Many published studies have documented increased LTE<sub>4</sub> levels in patients with infectious diseases due to respiratory syncytial virus (RSV), such as bronchitis, pneumonia, and bronchiolitis, suggesting that LTs may be involved. Cys-LTs, in fact, are released during RSV infection and may contribute to the inflammatory state [45]. In a 36 mo, double-blind trial, 130 infants (median age: 9 months) who were hospitalized with acute RSV bronchiolitis were randomized into 2 parallel comparison groups of 5 mg montelukast chewable tablets or matching placebo given for 28 days starting within 7 days after the onset of symptoms. Infants in the montelukast group were free of symptoms on 22% of the days and nights, which was significantly lower than the placebo group, and there were significant reductions in day-time coughing and clinical exacerbations compared to the placebo [46–49].

## 3. Allergic conjunctivitis and the possible role of nasal allergy

The incidence of 'allergic conjunctivitis' and its particular forms vary [50–54]; seasonal allergic conjunctivitis (SAC) occurs most frequently, followed by atopic kerato-conjunctivitis (AKC), vernal kerato-conjunctivitis (VKC) and perennial allergic conjunctivitis (PAC), whereas giant papillary conjunctivitis (GPC) may be seen only sporadically. SAC and PAC appear in relatively milder form, whereas AKC and VKC occur in a more severe bilateral form, where the conjunctivae and cornea may also be affected [50,54] the coexistence of allergic rhinitis and conjunctivitis has repeatedly been reported in the literature [50–56].

An allergic reaction initially occurring in the nasal mucosa may affect the conjunctiva in different ways upon involving diverse mechanisms: (i) this reaction leads to release of mediators, cytokines and other factors, which can then penetrate to the conjunctiva through the naso-lacrimal duct [51–58]; (ii) the released factors can also be transported to the conjunctiva by the local haematologic ways (a. maxillaris- pars

pterygopalatina, v. facialis, plexus pterygoideus) [51–60]; (iii) allergic reactions in the nasal mucosa can stimulate the local neurogenic network and released neuropeptides may reach conjunctiva along and/or through the appropriate nerves (n. trigemini, n. nasociliaris, pterygopalatine ganglion) [61–63]; and (iv) this reaction and released factors can stimulate the local nasal mucosal lymphatic system, ‘nose-associated lymphatic tissue’ (NALT), which is able to communicate with the lymphatic tissue of the lacrimal system, ‘tear duct-associated lymphatic tissue’ (TALT), ‘lacrimal drainage-associated lymphoid tissue’ (LDALT), ‘eye associated lymphatic tissue’ (EALT) and that of the conjunctiva, called ‘conjunctiva-associated lymphatic tissue’ (CALT) [57–59,63–66]. In this way not only transmission of certain signals but also cellular traffic of various cell types, for example, T lymphocytes (Th1 and Th2) and B cells (plasma cells), can also be realized [50,56,59,60,67–73]. An additional mechanism that could also play a role in the cellular traffic among the particular organ-associated lymphatic tissues is the ‘defective homing’ of the B lymphocytes [59,74]. Nasal provocation tests (NPTs) combined with registration of the conjunctival parameters are able not only to show the causal role of a certain allergen in the nasal mucosa and subsequently in the conjunctiva, but also to record quantitatively responses in their dynamic and time-related course. Although the NPTs are a laborious, time-consuming technique and require special apparatus and facilities, they generate important clinical data that cannot be gathered by other tests. By combining of the recorded parameters, NPTs are also able to confirm a causal role of one organ in a response of another organ, in this case the causal relationship of nasal mucosa and nasal allergy in the reactions of the conjunctiva. Significant correlation of the first and repeated NPTs confirms reliable reproducibility of this technique. NPTs can also discriminate between the participation of the allergy and the non-specific hyperactivity in the patient’s complaints. Similar motivation is applicable for the conjunctival provocation tests (CPTs) with allergens showing an allergic reaction directly in the conjunctiva and its causal participation in the conjunctival complaints [75]. Our results emphasize some important clinical implications. As nasal allergy can induce a secondary conjunctival response (CR), allergic rhinitis may not always be seen only as a co-existing disorder to allergic conjunctivitis, but in some patients as a causal trigger for the allergic conjuncti-

vitis. This fact would implicate existence of two forms of allergic conjunctivitis, a ‘primary or classical form’ in which the initial allergic reaction and the subsequent steps (clinical symptoms) take place exclusively in the conjunctiva, whereas the ‘secondary form’ may be induced by an allergic reaction occurring initially in the nasal mucosa and only the consequences (clinical symptoms) are displayed by the conjunctiva [59, 69].

#### **4. The ocular allergic response and the role of LTs in allergic conjunctivitis**

Particulate matter-pollutants, pollen, dust, mold, mite, animal dander, and other proteins, as well as dirt and sand, is meant to be blocked from reaching the eye by eyebrows, eyelashes, or eyelids. The particles that evade these barriers alight on the ocular surface and are buffered by the tear film, the most important barrier the eye has against foreign substances. Whatever is not washed away by the tear film eventually reaches the ocular surface. The ocular allergic response is caused by exposure of the conjunctiva, the mucus membrane that covers the posterior aspect of the eye, to an antigen. Immunologic recognition of intruders awakens the body’s defenses, leading to antigen recognition and sensitization, antibody activation, and a full-blown over-reactive immunologic response.

Dry eye and allergic conjunctivitis are chronic inflammatory diseases of the cornea and conjunctiva (ocular surface). Dry eye affects 5 million individuals in the United States alone and is more prevalent in women than men [76]. Allergy including seasonal allergic conjunctivitis, vernal keratoconjunctivitis, giant papillary conjunctivitis (also known as contact lens-induced papillary conjunctivitis), and atopic keratoconjunctivitis affects 20% of the population [56]. Hallmarks of these diseases are symptoms of ocular pain and discomfort, and signs of ocular surface inflammation that generate inflammatory cytokines and matrix metalloproteinases. These inflammatory mediators lead to death of the surface cells of the corneal and conjunctival epithelia [77].

The pathophysiological basis of conjunctivitis and other type I hypersensitivity disorders, such as, rhinitis, asthma and dermatitis, relies on the release of chemical mediators from inflammatory cells [78]. Histamine plays a pivotal role in ocular hypersensitivity reactions of both immunological and non-im-

munological origin, by exerting its effects on blood vessels, nociceptive nerves, fibroblasts, epithelial and goblet cells, mainly *via* histaminergic receptor activation in the ocular surface [79,80]. Histamine, being the main early activating molecule of the inflammatory cascade leads to the release of late phase reaction mediators, such as nitric oxide (NO) [81,82]. Additionally, the *de novo* synthesized pro-inflammatory cysteinyl leukotrienes (cysLTs) seem to be equally important, their release in tears from patients with various forms of conjunctival inflammation having been documented [83]. Thus, histamine, cys-LTs and NO are involved in the inflammatory processes associated with type I hypersensitivity reactions, which have two well-defined periods.

The pathophysiology of allergic conjunctivitis is not a simple process. New findings suggest that a wide range of cytokines, chemokines, proteases and growth factors are involved by complex interactions [84]. In allergic conjunctivitis, there is increased tear levels of several chemical mediators such as histamine, tryptase, leukotrienes (LTs) and prostaglandins [56]. In addition, tear levels of LTB<sub>4</sub> and LTC<sub>4</sub> were found to be significantly higher in patients with vernal keratoconjunctivitis than in controls [83].

Dartt DA et al. [85] showed that cysteinyl leukotrienes LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> produced in the conjunctiva during ocular allergy, dry eye disease, or other inflammatory diseases of the ocular surface stimulate goblet cell mucous secretion that can contribute to the excess mucous seen in these diseases. The chronic inflammation in these ocular surface diseases damages the cornea and conjunctiva, causing chronic pain from exposed nerve endings. They demonstrated that cysteinyl leukotriene stimulated goblet cell secretion was completely blocked by RvD1 and RvE1. Thus, resolution of inflammation by the production of proresolution mediators, namely, RvD1 and RvE1, can terminate excess goblet cell mucous secretion allowing the ocular surface to repair. These results also support the hypothesis that resolution of inflammation is an active process.

## **5. The use of leukotriene antagonists drugs in the treatment of allergic conjunctivitis**

Allergic conjunctivitis is a collection of hypersensitivity disorders that affect the lid, conjunctiva and cornea. It is characterized by immunoglobulin E (IgE)

mediated and/or T-lymphocyte-mediated immune hypersensitivity reactions [86]. These reactions are initiated by binding of an allergen with specific IgE on the surface of mast cells. The resultant mast cell degranulation leads to early phase and late phase responses. The early phase response develops immediately after exposure to the allergen with clinical symptoms and signs such as itching, chemosis and congestion. This is followed by the late phase response after 8–24 hours which is characterized by conjunctival cellular infiltrations particularly eosinophilia and neutrophilia [87]. The pathophysiology of allergic conjunctivitis is not a simple process. New findings suggest that a wide range of cytokines, chemokines, proteases and growth factors are involved by complex interactions [84]. In allergic conjunctivitis, there is increased tear levels of several chemical mediators such as histamine, tryptase, leukotrienes (LTs) and prostaglandins [56]. In addition, tear levels of LTB<sub>4</sub> and LTC<sub>4</sub> were found to be significantly higher in patients with vernal keratoconjunctivitis than in controls [83]. In fact, leukotrienes play a role in the development of seasonal allergic conjunctivitis as well as the more severe forms as vernal keratoconjunctivitis and atopic keratoconjunctivitis [84].

Treatment of allergic conjunctivitis includes several drug groups such as antihistamines, mast cell stabilizers, non-steroidal anti-inflammatory drugs and corticosteroids in resistant cases [50]. However, the increased worldwide prevalence of ocular allergy has stimulated expansion of management strategies towards physiologic and immunologic drug targets [8]. One of these targets is the leukotrienes [88]. The pro-inflammatory effects of leukotrienes have been well described in asthma and rhinitis. Leukotriene receptor antagonists have emerged as important therapeutic options that show clinical efficacy in treatment of bronchial asthma.

The ocular allergic response results from exposure of the conjunctiva to an environmental allergen and binding with specific IgE on the conjunctival mast cells. The resultant mast cell degranulation plays a key role in the pathogenesis of both the early and late phase responses of ocular allergy [84]. Compound 48/80 is a non-immunogenic mast cell degranulating agent that produces manifestations of external allergic inflammation when applied topically to the ocular surface [89]. The degranulation produced by the compound is less extensive but morphologically sim-

ilar to that seen in vernal and giant papillary conjunctivitis. Therefore, it can serve as a useful tool for testing ocular anti-inflammatory agents [90]. Studies with compound 48/80 applied topically to rabbit eyes, producing allergic inflammatory manifestations that were evident on clinical examination of the eye as well as on histopathological examination of conjunctival specimens, have been described in literature to show the efficacy of anti-leukotrienes drugs efficacy in the treatment of allergic conjunctivitis. El-Hossary and collagues [91] demonstrated that pretreatment of allergic conjunctivitis model rabbits with 0.1% montelukast eye drops exhibited improvement of ocular inflammatory manifestations both clinically and by histopathological examination. The improvement was more evident after 24 hours of compound application. In agreement with the results of this study, it was before described that oral montelukast for 15 days produced significant and persistent reduction of ocular signs and symptoms in asthmatic patients with vernal keratoconjunctivitis [92]. In addition, oral montelukast combined with oral cetirizine were effective in decreasing orbital congestion and inflammation in patients with thyroid eye disease [93]. Moreover, oral zafirlukast, another leukotriene receptor antagonist similar to montelukast, could significantly attenuate the development of conjunctival edema and inhibit the increase in the number of eosinophils in rats with experimental allergic conjunctivitis [94].

Regarding topical ocular application of these drugs, topical application of a leukotriene receptor antagonist in combination with a cyclooxygenase inhibitor could significantly improve inflammatory manifestations in rabbit eyes burned with sodium hydroxide [95]. In addition, Papathanassiou et al. [96] reported that topical application of zafirlukast to rat eyes, challenged with compound 48/80, produced significant inhibition of the late phase nitric oxide production of the conjunctival hypersensitivity response. The authors concluded that leukotriene receptor antagonists might contribute to the management of ocular inflammatory response. Outside the eye, inhaled montelukast could significantly inhibit the bronchoconstriction induced by LTC<sub>4</sub> and LTD<sub>4</sub> with no injury to the lung tissue in an animal model of asthma [97] and this demonstrates the therapeutic effectiveness and safety of locally applied montelukast.

Although leukotrienes play a role in development of allergic conjunctivitis, they are not the only mediators involved in this disease. Histamine, tryptase and

prostaglandins are also involved in the immediate allergic response [56]. In addition, mast cell degranulation induces activation of vascular endothelial cells and thus the expression of several chemokines and adhesion molecules that finally lead to the ocular allergic late phase reaction [84]. Moreover, conjunctival and corneal epithelial cells and fibroblasts may contribute to mounting the allergic inflammation by expressing and producing cytokines, chemokines, adhesion molecules and growth factors that maintain local inflammation and lead to tissue remodelling [98]. Montelukast was reported to significantly attenuate LT-induced degranulation of bone marrow derived mast cells [99]. The drug was also found to inhibit the expression of vascular endothelial growth factor and its receptors in lung tissue of experimentally induced asthma in rats [100]. Vascular endothelial growth factor is over expressed in vernal keratoconjunctivitis and may involve tissue growth and remodelling that occur in severe cases of this disease [101].

In El-Houssary's study [91], pre-treatment of allergic conjunctivitis model rabbits with 1% prednisolone produced more improvement of the allergic response than montelukast detected by significant decrease in the clinical score at all time intervals of examination and by marked improvement of the histopathological picture as the conjunctiva appeared fairly normal after 24 hours of compound application. Topical corticosteroids are very effective in the treatment of allergic conjunctivitis for their immunosuppressive way of action [102]. Therefore, it was expected that topical prednisolone was more effective than topical montelukast in the above mentioned study.

Despite the number of pharmacological agents currently used to prevent the clinical manifestations of ocular hypersensitivity, there are still continuing efforts aiming at the development of more efficacious topical medications to control the most severe episodes of the disease [103]. Currently, anti-LT therapies are approved only for patients with asthma [104], though recent reports support the clinical efficacy of cysLT receptor antagonists in patients with rhinitis [105, 106].

In conclusions, allergic conditions are common in all pediatric age groups, and significantly affect the health and overall quality of life of children and their families [107]. Also in their less severe forms, they often cause considerable disruptions to daily life for pediatric patients, including sleep disturbances; limi-

tation of activities; disrupted reading, computer work, or outside play; and impaired psychosocial functioning.

Early and accurate detection of ocular allergy syndromes in children presents a challenge in the primary care setting, as young children are often unwilling participants in ocular examinations. Involvement of pediatric ophthalmologists with specialized training and equipment may be necessary to avoid preventable vision loss in more severe cases. It is the responsibility of all involved to optimize the treatment of these children suffering from allergic disease.

Topical ocular montelukast can be a potential therapeutic drug with a new route of administration that can be used for treatment of allergic conjunctivitis.

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