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Review Article

Effectiveness of montelukast in pediatric patients with allergic rhinitis

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ABSTRACT

Allergic rhinitis (AR) is one of the most common chronic diseases of childhood and carries significant morbidity as well as physical and psychosocial consequences. Therapy aims to alleviate clinical symptoms, prevent complications and improve psychosocial consequences. Leukotrienes which are amongst the main mediators in pathogenesis of AR have chemotactic properties and lead to increased vascular permeability. Thus, leukotriene antagonism may be an effective therapeutic option in treatment of allergic diseases, specifically AR. Montelukast which is a leukotriene receptor type 1 inhibitor has variable efficacy in children with AR and the guidelines recommend its use in children with seasonal AR aged six years and above. Although its efficacy is inferior to anti-histamines and intranasal corticosteroids, combination treatment may warrant clinical efficacy. Therefore, montelukast may be considered to be a well-tolerated therapeutic option for children with AR with minor side effects though long term results need to be assessed.

In conclusion, larger scale research enrolling pediatric cases with seasonal and persistent AR are required before concise recommendations about montelukast use in pediatric AR can be made.

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1. Introduction

Allergic rhinitis (AR) is one of the most common chronic diseases of childhood with prevalence ranging from 7% to 30% in different parts of the world and more importantly this prevalence is increasing with time [1–4]. Despite low mortality the disease is associated with significant morbidity. Some of the physical complications of AR in children include otitis media with effusion,

chronic or recurrent rhinosinusitis and coexistence of asthma [5,6]. Besides physical complications, pediatric AR is associated with disturbance of sleep, psychosocial problems, decrease in school performance due to absenteeism, learning difficulties and distraction as well as impairment in overall quality of life [5–9]. Thus, high prevalence and significant morbidity makes AR and its treatment a topic of research interest. Unique characteristics of the pediatric age group such as differences in maturity of drug metabolic pathways, long term favorable results of early treatment before complications develop and ethical issues in carrying out clinical trials necessitate treatment recommendations different from adults.

Main targets in treatment of pediatric AR are to alleviate the physical symptoms, prevent development of complications and to

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improve psychosocial and functional consequences without significant side effects [10]. Treatment of pediatric AR consists of allergen avoidance, pharmacotherapy and immunotherapy [10,11]. Antihistamines and nasal corticosteroids constitute the mainstay of classical pharmacotherapy, but newer agents such as leukotriene antagonists are being investigated with conflicting results [10,11].

Leukotrienes which are inflammatory mediators synthesized from arachidonic acid are amongst the major mediators that take part in the pathogenesis of AR similar to other allergic diseases and are produced by a variety of inflammatory cell types such as mast cells, eosinophils and basophils [11,12]. Upon, activation of cysteinyl-leukotriene receptors (LTR), inflammatory cells are activated and recruited to the area and vascular permeability is increased. Moreover, cysteinyl-leukotrienes induce bronchial hyper-reactivity and airway remodeling [13]. Thus, antagonism of leukotrienes is expected to be an effective treatment for allergic diseases especially in cases where AR coexists with asthma.

Montelukast is a selective antagonist of LTR type 1, thus inhibit the proinflammatory actions of cysteinyl-leukotrienes such as leukotriene D4 [12,13]. Moreover, montelukast has been demonstrated to have anti-inflammatory actions independent of antagonism of cysteinyl-leukotrienes such as inhibition of 5-lipoxygenase enzyme activity and eosinophil adhesion and migration [13]. These mechanisms of actions have made montelukast a popular candidate in treatment of many different allergic diseases. Therefore, its use was first approved for pediatric asthma and then AR.

2. Efficacy of montelukast in pediatric allergic rhinitis

In general, montelukast has been reported to cause symptom improvement in AR although its effects were inferior to antihistamines and intranasal corticosteroids [14]. This has led to the recommendation of montelukast especially in treatment of seasonal AR in children aged six years and above in ARIA guideline [11,15]. Similarly, combination treatments that include montelukast with anti-histamine or intranasal corticosteroids led to clinical improvement in AR [14]. Pediatric age group constitutes the special subgroup discussed in this review but the results of the research yield conflicting results with different outcomes.

2.1. Montelukast versus placebo

A double blind randomized placebo-controlled trial by Philip et al. [16] enrolled patients with a wide age range including the adolescents over 15, demonstrated that montelukast treatment and anti-histamine treatment resulted in improvement of day and night-time nasal and ophthalmologic findings of AR when compared to the placebo but anti-histamine and montelukast arms were not compared [16]. A randomized double blind parallel group study on children with AR by Razi et al. [17], demonstrated that montelukast treatment improved day time nasal and eye symptom and decreased eosinophil counts compared to the placebo [17]. Moreover, in children with pollen induced AR, montelukast treatment either as monotherapy or in combination with antihistamines was found to improve nasal obstruction in late phase of nasal challenge [18]. Therefore, we can state that montelukast seems to improve clinical symptoms of AR in children when compared to untreated children.

2.2. Montelukast versus nasal steroid

Nasal steroids are the mainstay of treatment in pediatric AR [11]. A study by Di Lorenzo et al. [19] which included patients aged

above 12 years failed to demonstrate a significant difference between fluticasone nasal spray monotherapy and fluticasone nasal spray – montelukast combination therapy [19]. Similarly, nasal mometasone monotherapy was found to result in greater improvement in AR symptoms in children compared to montelukast monotherapy as well as a greater decrease in interleukin5/interferon γ ratio in nasal lavage fluid [20]. These results indicate that montelukast treatment in children with AR seems to add little, if any, benefit over nasal steroid treatment. However, the number of studies that addressed the question is low and we need further research on the topic.

2.3. Montelukast versus antihistamine

There are conflicting results about the clinical efficacy of montelukast treatment in pediatric AR compared to antihistamine treatment. As monotherapy, montelukast was found to result in similar clinical improvement and nasal lavage cytokine levels compared to antihistamines in 24 children with persistent AR aged 6–12 years [20]. On the other hand, in a study of 60 children aged 6–12 years age with persistent AR, Chen et al. [21] demonstrated that both cetirizine and montelukast monotherapies were superior to placebo in AR symptom relief. Upon assessment of clinical efficacy based on total symptom score (T4SS), cetirizine was superior to montelukast. On the basis of individual symptoms, improvement in night time symptoms was higher for montelukast treatment when compared to cetirizine while improvement in nasal itching was higher for the latter. Moreover, they have demonstrated that nasal airway resistance and nasal smear eosinophilia decreased with both cetirizine and montelukast treatment while serum IgE and eosinophilic cationic protein did not significantly change [21].

Antihistamines were found to decrease symptoms associated with perennial AR in children as monotherapy or in combination with montelukast but inflammation reflected by exhaled nitric oxide levels decrease only when antihistamines are combined with montelukast or inhaled steroids [22].

Antihistamine monotherapy was found to have similar efficacy in nasal symptom score, quality of life and nasal flow when compared to antihistamine and montelukast combination treatment. However, montelukast combination was better in reducing pulmonary symptoms and improving lung function tests in children with grass pollen induced AR [18]. Similar results were reported from a study which enrolled children with persistent AR; montelukast addition to antihistamine treatment led to better improvement in nasal congestion but the difference in improvement of other AR symptoms was not significant between antihistamine monotherapy or montelukast-antihistamine combined treatment [23].

Montelukast treatment has been reported to improve some of the clinical outcomes in children with asthma although inhaled corticosteroids remain to be the mainstay of treatment [24]. It has been demonstrated that in children with stable asthma and persistent AR, addition of montelukast to antihistamine treatment leads to more rapid improvement in clinical symptoms such as sneezing. Addition of montelukast to antihistamine results in a greater nasal volume measured by acoustic rhinometry in this specific group of children [25].

Thus, montelukast seems to provide better relief of inflammation in children with AR compared to antihistamines alone however, both drugs have their advantages in improvement of different clinical symptoms. Therefore, the choice of montelukast, antihistamine or combination of the two drugs in treatment of AR in children needs to be personalized based on the dominant clinical symptom of the child.

3. Safety of montelukast in pediatric allergic rhinitis

Montelukast has been reported to be a well tolerated and safe therapeutic option for children. Most common adverse reactions reported include upper respiratory tract infection, headache, pharyngitis, abdominal pain, nausea and vomiting. Moreover, elevations of serum alanine and aspartate transaminase elevations have been documented. However, these adverse reactions were found to occur in similar frequencies between montelukast and placebo groups in different studies [26].

Montelukast treatment in children has been reported to be associated with few and mild side effects. In an article by Bisgaard et al., seven studies performed by Merck Research Laboratories, involving a total of 2751 children with asthma or allergic rhinitis aged 6 months to 14 years, were reviewed and adverse reactions were reported to be similar to placebo and similar care modalities [27,28]. In addition, side effects associated with montelukast treatment were reported to be similar to placebo and antihistamine treatment in a double blind randomized placebo-controlled study by Philip et al. [16]. Di Lorenzo et al. did not report side effects in detail for his double blind placebo controlled parallel group study, however recorded that all were mild in severity [19].

Concerns exist about the association of montelukast treatment with suicidality. In a review by Philip et al., two methods were used to investigate for possible suicide or self-harm behavior. In the first part of this review, 116 pediatric and adults studies were included and summaries of investigator reported adverse reactions were identified. In the second part of the review, they included 41 double blind placebo controlled studies and identified both investigator reported adverse reactions and other events in study databases that are described as self-harm behavior. The analysis failed to demonstrate a significant difference in the rate of self-harm and suicide behavior in patients receiving montelukast compared to antihistamine or placebo. However, this study did not analyze the pediatric subgroup separately [29]. In another study by the same group, Merck clinical trial data was retrospectively analyzed to compare behavior related side adverse events in patients receiving montelukast or placebo and the results revealed that the frequency of these events were rare and not significantly different between patients receiving montelukast or placebo. They failed to detect a difference in pediatric subjects in terms of behavior related side effects compared to adult patients [30].

In conclusion, current literature suggests that montelukast is more useful in treatment of pediatric AR when used in combination with conventional pharmacological agents such as antihistamines and nasal steroids. The results of efficacy studies are conflicting in their results and variable in the specific clinical characteristics of the patients enrolled such as the coexistence of asthma with AR. Montelukast seems to yield better improvement in some of the clinical characteristics such as nasal obstruction and sneezing in pediatric AR but not cause much change in other symptoms when compared to conventional therapeutic modalities. Thus larger scale researches enrolling pediatric cases with intermittent and persistent AR are required before concise recommendations about montelukast use in pediatric AR can be made and before long term safety is warranted.

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