



MANAGEMENT OF ASTHMA WITH MONTELUKAST

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ABSTRACT

Respiratory tract disorder is a very common problem faced by pediatric population, asthma being one of the most common chronic disorders in young children. Many preschool children regularly wheeze, especially during common cold infection and cold seasons. Some children wheeze after a simple exercise or some after the introduction of medication like aspirin or after introduction to allergens. An anti-inflammatory therapy, consisting mainly of inhaled corticosteroids (ICs) has been the main treatment of asthma since the beginning and it still remains the first line therapy in asthma management. Since Leukotriene (LTs) are chemical mediators of airway inflammation in asthma, Leukotriene receptor antagonist (LTRAs) can be a potent anti-inflammatory drugs in the long term treatment of asthma. There are different LRTA medicines, but mainly Montelukast can be used in pediatric population, that can decrease the airway inflammation and provide bronchoprotection. The safety profile, oral administration as single daily dose and better compliance is the highlight of this drug. In this review, we describe the advances on the use of montelukast in the treatment of asthma.

Keywords: montelukast; asthma; children

INTRODUCTION

Asthma is a very common childhood disorder. It is a chronic inflammatory condition of airways resulting in bronchospasm and episodic obstruction. Its characteristic feature is bronchial hyper-responsiveness to stimuli and causes bronchoconstriction, predominantly by their action on effector cells such as smooth muscle. Indirect stimuli such as exercise, cold air and hyperosmolar aerosol such as mannitol and hypertonic saline provoke bronchospasm through the release of mediator from inflammatory cells. Many symptomatic children loses their symptoms after the age of 5 to 6 yr but there are many for whom it still remains the burden and also for the family.

The medical treatment of asthma began more than 50 yrs ago and till date the mainstay of treatment still remains the same as before and it is inhaled corticosteroids and B2-agonists bronchodilators. The treatment mainly focuses on reducing airway inflammation by minimizing proinflammatory environmental exposures using daily medication. Inhaled corticosteroids are the most effective treatment of asthma and it has long been used as the first line therapy. However, there are some groups of population of asthma that are resistant to inhaled corticosteroids (ICS) and large group of patients remains symptomatic despite treatment and need other medication as monotherapy or add on therapy. Montelukast is a leukotriene receptor antagonist that has been shown to be effective as monotherapy or as an add-on therapy for the treatments of asthma, in those whose symptoms are not well controlled with ICS therapy.

Leukotriene modifiers (LTRs):

Leukotrienes are chemical mediators of asthmatic airway inflammation. They are formed from arachidonic acid, which are derived from the action of phospholipase A2 and they are released by eosinophils, mast cells, neutrophils, lymphocytes, macrophages, and basophils. Arachidonic acid is metabolized by two major pathways, the cyclooxygenase pathway (forming prostaglandins and thromboxanes) and the 5-lipoxygenase pathway (producing leukotrienes). The cysteinyl leukotrienes LTC4 and LTE4, are found to play very important role in the pathophysiology of asthma. The leukotriene receptor antagonists (LTRAs) selectively block the binding of cysteinyl leukotrienes to the CysLT1 receptor. This receptor was found to be the receptor through which most of their actions are mediated like bronchospasm, mucus hypersecretion and eosinophil migration and increased vascular permeability (1). Consequently, the LTRAs inhibit bronchconstriction. Moreover, LTRAs prevent many types of provoked asthmatic responses, including allergen-induced, exercise- and cold-air-hyperventilation-induced, and aspirin- induced asthma. Three drugs of this class are in use at present – zafirlukast, pranlukast, and montelukast.. Only montelukast has been extensively studied in children and proven to be safe and effective in children. Pediatric studies on montelukast found that it is well tolerated. The majority of the reported adverse effects were mild. In clinical trials the incidence of these adverse effects was not higher than with placebo.

Montelukast as a Management of childhood asthma:

For the past few decades, we have been using inhaled corticosteroids and B2-agonists bronchodilators for the treatment or management of asthma. No new therapy has been introduced or developed and we are still bound to use the same old protocols to control it. Inhaled corticosteroids and B2-agonists bronchodilators remains the first and second lines of therapies for past few decades. Certain groups of population of asthma sufferers are becoming resistant to these drugs. The side effect of continuous use of these drugs still remains a big concern, particularly with the high doses. And also, some patients finds it hard to use the inhalation route of administration of drugs and ensuring adequate and correct dosing is a concern. In such cases, montelukast overcomes ICS and B2-agonists as it has an advantage of oral administration, once daily dosing protocol and has properties of bronchodilation. Such properties of montelukast makes it a new drug of interest in the treatment of asthma. Montelukast improves symptoms, rescue medication use and pulmonary function, and reduced the rate of exacerbation and the level of blood eosinophils, in mild-to-moderate asthmatics, as proven by many clinical trials.

Several randomized trials have been performed in the treatment of asthma comparing montelukast with placebo. Comparing montelukast with placebo, the result showed that the drug helps the patients suffering from mild to moderate symptoms and helps improve day time asthma symptoms like cough, wheeze, difficulty in breathing and activity limitation. At the same time, the overnight asthma symptoms, the duration suffering days, the need of increasing dosing of ICS and B2agonist were also decreased. The laboratory investigations suggested that there is a marked improvement in the peripheral blood eosinophil, forced expiratory volume in 1 second (FEV1) and fractional exhaled nitric oxide (FeNO) in the montelukast population(2). A study after conducting a randomized controlled trail, concluded that montelukast provides clinical significance in controlling asthma symptoms and helps improve morning FEV1 (3)(4). A randomized controlled trial with montelukast 5 mg for 4 week concluded that the medicine helps in suppressing sputum eosinophilic cationic protein, sputum eosiniphilic count and fractional exhaled nitric oxide and improves asthma symptoms(5). Another randomized controlled trails with children of 6 to 14 yrs with montelukast for 8 weeks concluded the similar improvements in asthma symptoms and improvement in FEV1(6). Similar improvement and reduced exacerbation was seen after a randomized controlled trail performed with children of 2 to 5 yr with montelukast for longer duration of time (7). A study conducted among preschool children revealed that 4 weeks treatment with montelukast resulted in a decrease in bronchial hyperreactivity compared with placebo (8).

Another randomized, double-blind, placebo-controlled, parallel-group trial was performed among 689 patients (228 placebo group and 461 montelukast group). Overall, approximately 60% of patients were boys and approximately 60% were white. Patients were relatively evenly divided by age: 21%, 24%, 30%,

and 23% were aged 2, 3, 4, and 5 years, respectively. For about 77% of patients had history of asthma symptoms that had first developed during the first 3 years of their life. During the placebo baseline period, patients had asthma symptoms on 6.1 days/week and used B2-agonist on 6.0 days/week. There were no clinically important demographic differences between the 2 treatment groups. Seventy-one patients (26 from placebo group and 45 from montelukast group) did not complete the study. In the placebo group, 12 patients were withdrawn because of protocol deviations, 7 stopped treatment because of adverse effects, 4 withdrew consent, 2 were lost to follow-up, and 1 stopped treatment because of an elevated alkaline phosphatase value. In the monte-lukast group, 12 were withdrawn because of protocol deviations, 16 patients stopped treatment because of adverse effects, 8 withdrew consent, 7 were lost to follow-up, and 1 each discontinued because of lack of efficacy and an error by the study center. A total of 12 and 17 patients in placebo and montelukast groups, respectively, were excluded from 1 or more efficacy analyses because they lacked baseline or treatment period data. Over 12 weeks of treatment, the percentage of days with daytime asthma symptoms was significantly lower and the percentage of days without asthma was significantly higher in the montelukast group compared with the placebo group. Moreover, the improvements for the montelukast group in overall daytime asthma symptom scores and in individual symptoms scores for cough, wheeze, trouble breathing, and activity limitations were significantly greater than those for the placebo group. Furthermore, the percentage of days on which B2-agonist was used and percentage of patients requiring oral corticosteroid rescue were significantly lower in the montelukast group (9).

Another 8-week trial of 336 children 6 to 14 years old with intermittent or persistent asthma was conducted which found that 5 mg of montelukast nightly increased mean morning FEV1 significantly more than placebo (approximately 8% vs 4%) (10). In the group, Short-acting B2-agonist use decreased by 0.57 puffs daily among montelukast-treated children and increased by 0.22 puffs daily among placebo-treated children.

Another trial studied patients with mild to moderate asthma and made a conclusion that montelukast administration was associated with dose-related improvements in asthma control end points. Improvements were seen in FEV1 and peak expiratory flow rate and in daytime symptom scores, use of as-needed inhaled B2-agonists, and asthma-specific quality of life (11). A study reported that montelukast permitted a 47% reduction in inhaled corticosteroid dosage compared with a 30% reduction with placebo in a group of asthma patients previously well controlled on inhaled corticosteroids (12).

Many studies compared montelukast with corticosteroids. Those studies mainly focuses on specific outcome like pulmonary function, symptoms and rate of exacerbations and the majority of studies have confirmed the greater efficacy of low dose ICS against montelukast (13)(14) . Because of this reason, many institutional guidelines state that ICS are more effective than LTRAs as monotherapy for asthma management. And, montelukast becomes the latter choice . But the majority of the these studies were done in cases with

patients who had frequent symptoms and poor pulmonary function and thus ICS was expected to be more effective than montelukast. Montelukast was still more effective than placebo when the selected patients had mild asthma(15). At doses equivalent to 500 mg daily of beclomethasone, LTRAs were less effective than ICS on symptoms, pulmonary function and sputum eosinophils (16)(17). However, in a study of 534 patients with mild asthma well controlled by low-dose ICS, when replacing it with montelukast, was found to have good asthma control in over 75% of cases after 6 weeks, with an increase in compliance to treatment (18). Some trials concluded that Mild-to-moderate chronic asthmatic patients treated with LTRAs were 60% more likely to experience an asthma exacerbation requiring oral steroids than those treated with ICSs (19)(20). But in most this trials the daily dose of ICSs was 400 mg of beclomethasone or equivalent. After 6 weeks of treatment, the patients using ICSs showed more improvement in clinical symptoms and FEV1. The use of montelukast as a mono therapy in asthma remain a doubt and the patients using montelukast is more likely to suffer an exacerbation requiring systemic steroids (20). On the other hand there aren't enough researches to conclude the advantage of ICSs over montelukast and further studies need to be done.

A study evaluated the efficacy of montelukast versus budesonide, mostly in preschool age group with mild persistent asthma, and found no differences between the two groups as far as drug tolerability, time to first additional anti-asthma medications and time to first severe exacerbation over a 52 weeks-study period (21). Other RCT also assessed the efficacy of montelukast or fluticasone given as monotherapy versus placebo for three months and many such studies have concluded that both drugs decreased asthma-like symptoms and improved the daily symptoms score, even though fluticasone appeared more effective than placebo. Some studies showed that montelukast added to the usual treatment with ICS reduced the risk of worsening asthma symptoms and unscheduled physician visits during the annual September asthma epidemic. Some studies even showed children treated with montelukast and fluticasone as monotherapy, showed that both drugs decrease rescue medications use and hospital visits. In particular, in children aged 2 to 5 years, montelukast was associated to less emergency visits compared to subjects aged 6 to 14 years. The findings suggest that montelukast could be beneficial to preschool and school going children suffering from asthma.

There are limited studies that compares the advantage of montelukast over long acting beta agonist (LABA) or vice versa. One study found that FeNO levels were significantly higher after salmeterol add on treatment compared with both placebo and montelukast (22). Other trial concluded that montelukast as an add-on therapy with ICSs provide equivalent result compared to salmeterol (23). The study conducted among children has revealed that add on therapy with montelukast plus low-dose budesonide was more effective than the addition of LABA or doubling the dose budesonide for controlling FeNO in asthmatic children (24).

Histamine and cysteinyl leukotriene are the inflammatory mediators that are released during exercise. Evaporation of water on the airway surface, during exercise, is the stimulus for their release (25).

Exhaled breath condensate Cys-LT values are shown to be higher in asthmatic children with EIB (exercise induced bronchospasm) and correlate with the decrease in FEV1 after exercise (26). LTRAs decreases exhaled LTE4 in atopic children with asthma(27). Accordingly, montelukast was found to be effective in controlling asthma symptoms after exercise in children. It is approved for the prevention of EIB from 2 years of age(28). Clinical datas have shown that once-daily treatment with montelukast (5 or 10 mg tablet) can offer protection against EIB within 3 days for some patient.

The cysteinyl leukotrienes are the leading mediators of the reaction that occurs in persons with aspirin-sensitive asthma after exposure to aspirin(29). LTRs resulted in almost complete inhibition of aspirin-induced bronchoconstriction as well as symptoms of the skin and gastrointestinal tract (30). For this reason LTRs are the treatment of choice for these patients (31)(32). Few studies also support the fact that montelukast effectively reduces acute asthma episodes if started before the viral season, when the exacerbation rate is higher.

A study done with asthmatic children who were aged 2–5 years showed that the response of administration of 5 mg/day of montelukast for two days protects against cold air-induced bronchial hyperreactivity(33). Similar finding was later confirmed in such patients who showed a significant decrease in methacoline-induced bronchial reactivity after a four weeks treatment with montelukast (34). In atopic children with asthma, monotherapy with montelukast for 28 days showed effectiveness for reducing airway resistance and bronchial inflammation(35), and for improving lung function and symptoms score(36). An Australian RCT conducted in children having mild intermittent asthma and the study showed that a short course of montelukast, introduced early at the first signs of an asthma episode, resulted in a significant reduction in acute health care resource utilization, symptoms, time off from school, and parental time off from work (37).

Another study showed that a 1-year course of montelukast in children with virus-induced asthma significantly reduces asthma exacerbations and the use of rescue medications. This study remains one of the few RCTs (random controlled trials) in preschool children with mild intermittent asthma that proves that prolonged treatment with montelukast reduces the consumption of ICS at 39.8% (38)

Obesity is also considered as a risk factor for asthma. It also plays an important role in poor asthma control through different mechanisms (39). Such obese patients often faces airway inflammation, though to a low degree and their symptoms are poorly controlled by ICS. A study suggests that in such cases, montelukast may be more effective than ICS. (40).

Adverse effect of montelukast:

A variety of studies shows that montelukast is well tolerated by children and adults. There are few

reported adverse effects but they are generally mild and includes headache, nausea, vomiting, abdominal pain, pharyngitis and ear infection. Over dose of montelukast may be associated with thirst, mydriasis and somnolence (41). Since the beginning of the use of montelukast, several case reports on the occurrence of a Churg-Strauss syndrome (CSS) have been reported. This is thought to be due to reduced steroid dosage but not related to montelukast. In addition, the fact that CSS has developed not only with montelukast, but also with zafirlukast and pranlukast, suggests that the syndrome may be related to the effect of antileukotriene drugs on leukotriene receptors. In clinical trials the incidence of these adverse effects was not higher than with placebo (42). No dose adjustment with montelukast is necessary for patients with renal and mild-moderate hepatic dysfunction. It crosses the placenta and is excreted in breast milk. Montelukast should not be prescribed to pregnant and lactating women, due to lack of controlled trials.

CONCLUSION

The current evidence indicates that first-line monotherapy with montelukast is still controversial and generally not used in asthma sufferers, with perhaps the exclusion of those who have aspirin-intolerant asthma and exercise-induced asthma and asthma in obese children. It has shown good effect in some cases of mild asthma but its use as monotherapy in severe form still remains to be studied. The addition of montelukast in patients whose symptoms remain uncontrolled by ICSs could provide equivalent clinical control to salmeterol. It has shown a very good outcome as an add-on therapy. Montelukast reduces short-acting B2 stimulant requirements in patients with chronic asthma and allows the dose of inhaled steroids to be reduced. Montelukast may be valuable in those asthmatic patients who find it difficult to use inhaled medications. Oral montelukast (4-mg chewable tablet) administered once daily is generally well tolerated without clinically important adverse effects in preschool children. Additionally, montelukast improved multiple exploratory efficacy end points, which is consistent with clinically important improvements in the treatment of asthma. Moreover, the results of these studies are consistent with and confirm results seen in studies pediatric patients above 6 yrs. Many studies demonstrated its safety in pediatric population above 2 yrs of age. Its safety and efficacy in young pediatric population (less than 2 yr) still need to be studied further.

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