

Montelukast in General Pediatric Practices

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Allergic diseases, e.g., allergic rhinitis, atopic dermatitis and asthma, are common problems in children. Researches on the pathogenesis of allergic diseases have led to the development of new specific antiinflammatory medications, including Montelukast, which blocks the interaction of cysteinyl leukotrienes to their receptors and resulting downstream events. Several studies have demonstrated the effect of regular Montelukast therapy on asthma, allergic rhinitis, viral-induced wheezing in bronchiolitis and chronic rhinitis symptoms. Evidence base medicine now shows that Montelukast can be used as a monotherapy in mild persistent asthma and can be an add-on drug to inhaled corticosteroid (ICS) in moderate to severe persistent asthma. Even in allergic rhinitis, Montelukast has a role in controlling rhinitis symptoms. Montelukast demonstrated a safety profile similar to placebo and more safety than ICS. Moreover, Montelukast can improve quality of life in patients with asthma and comorbid allergic rhinitis.

Keywords: Montelukast, Allergic rhinitis, Asthma, Viral-induced wheeze, Non AR

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Nowadays, the prevalence of childhood allergic disease and the mortality are increasing, even though there are many effective medications available. Allergic rhinitis, atopic dermatitis, asthma are also IgE-mediated disease and leukotrienes play a key role in their pathogenesis. The use of leukotriene receptor antagonist for the treatment of allergic disease is drawing more attention. Several studies show effectiveness of these medications.

Leukotriene Receptor Antagonists (LTRA)

Leukotriene receptor antagonists in Thailand that have been launched were Montelukast (Singulair) and Zafirlukast (Accolate) which are new medications that antagonized chemical mediators: leukotriene produced from activated mast cell at cysteinyl leukotriene₁ receptor that contributes to chronic inflammation, so it was claimed to have anti-inflammatory effect. The efficacy and safety of Zafirlukast is less than Montelukast, most studies in children contribute to Montelukast. Cysteinyl leukotriene is one of important mediators in allergic disease which has 5000 times more potency

than histamine, it causes bronchoconstriction, nasal blockage and increase mucous secretion.⁽¹⁾ Reviews from several studies support that Montelukast is effective in the treatment of the following allergic diseases in children:

1. Asthma

1.1 Compared with placebo

Van Schaik SM⁽²⁾ studied cysteinyl leukotriene (LTs) in respiratory secretion in children and found that quantities of LTs were significantly increased in secretion of children with acute bronchiolitis and recurrent wheezing more than children with upper respiratory infection.

Bigard et al⁽³⁾ studied the efficacy of Montelukast (4 mg) in the prevention of viral-induced asthma exacerbation in children 2-5 years old. Over 12 months of therapy, Montelukast significantly reduced the rate of asthma exacerbations by 31.9% compared with placebo and also the use of inhaled corticosteroid without any adverse events.

Knorr B et al⁽⁴⁾ found that Montelukast (5 mg) improved morning FEV₁ in 336 children aged 4-6 year-old with chronic asthma during 8 weeks.

Robertson C presented poster at American Thoracic Society (ATS) 2004 about the study in children aged 2 - 14 years old with mild intermittent asthma

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who did not regularly use antiasthmatic medications. The parents were advised to give Montelukast when the children had a cold or acute asthma exacerbation for at least seven days and not more than twenty days or until the symptoms were resolved within 48 hrs. The symptoms were daily recorded and the parents had to visit the doctor two weeks after the exacerbation for replace the medications for the next usage.

The result showed that the parents self management of the child's illness in active medication group was better than placebo groups. The patients in this group can decrease emergency visit to 25%, decreased the rate of absence from school to 37% and parents absence from work to 33%. Montelukast, chewable tablet, was easily used with good compliance and efficacy in young children without any side effects.

1.2 Compared with inhaled corticosteroid (ICS), inhaled cromolyn

Pavord ID et al⁽⁵⁾ found that inhaled corticosteroid used in asthmatic patients could not decrease sputum cysteinyl leukotriene even the absence of exacerbation and it was significantly increased greater than normal population within 48 hrs of acute exacerbation.

Volovitz et al⁽⁶⁾ studied a 4-week treatment of Montelukast (5 mg) in asthmatic children compared with inhaled cromolyn (8 mg/day) and found that Montelukast significantly reduced the concentration of leukotrienes (LTC₄) in the respiratory tract of children with persistent asthma whereas cromolyn could not reduce the concentration of leukotrienes.

Bukstein DA et al⁽⁷⁾ studied the use of Montelukast compared with inhaled fluticasone in asthmatic patients for one year. He found that oral Montelukast and inhaled fluticasone had similar efficacy in the control of the symptoms, whereas the use of antibiotic was less in Montelukast group and the compliance in Montelukast group was significantly higher.

Garcia ML et al poster presented in European Respiratory society (ERS) 2004 that the efficacy of Montelukast was similar to inhaled fluticasone in controlling asthmatic symptoms but the growth rate was significantly higher in the Montelukast group.

Allen-Ramey FC presented in the American Congress of Allergy Asthma and Immunology (ACAAI) 2003 found that children aged 2-5 years old and 6-14 years old, the efficacy of Montelukast was similar to inhaled fluticasone in controlling asthmatic symptoms

in both groups but the rate of emergency visit in the younger was lower in Montelukast group than inhaled fluticasone.

1.3 Add-on drug with inhaled corticosteroid (ICS) and other controller medications

Travier et al poster presented in European Respiratory society (ERS) 2004 had studied the use of Montelukast with ICS compared with long acting β_2 agonist (LABA) with ICS in children 6-14 years old for 12 months, he found that Montelukast with inhaled corticosteroid decreased the use of short acting β_2 agonist, oral corticosteroid for asthmatic attack and decreased the use of intranasal steroid in asthmatic patient comorbid with allergic rhinitis when compared with LABA and ICS.

2. Allergic rhinitis with asthma

Corren J et al⁽⁸⁾ reported that allergen challenging of nasal mucosa in allergic patients can cause bronchial hyperresponsiveness by measuring the decrease of PC₂₀ at 0.5 hour and 4.5 hours.

Gaga M et al⁽⁹⁾ found that the number of eosinophils in nasal mucosa of asthmatic patients with or without comorbid of allergic rhinitis was significantly increased more than normal population.

Settipane et al⁽¹⁰⁾ followed up allergic rhinitis patients for 23 years and found that the incidence of asthma was 2.3 times in allergic rhinitis patients when compared to normal population.

Thomal M et al⁽¹¹⁾ found that asthmatic patients with comorbid allergic rhinitis had greater prescription of bronchodilator and steroid usage, experienced more doctor visits and hospitalizations for asthma than did children with asthma alone.

Philip G et al⁽¹²⁾ studied the efficacy of Montelukast 10 mg daily for 2 weeks in 831 allergic rhinitis patients compared with the placebo group. The results showed that Montelukast had significantly reduced daytime and nighttime nasal symptoms and even β_2 agonist usage.

Price DB et al⁽¹³⁾ studied Montelukast 10 mg plus inhaled budesonide 800 μ g /day compared with budesonide 1600 μ g /day in 889 patients aged 15-75 yrs for twelve weeks, the study showed that morning PEF_R improved significantly but there was no difference in both group. But the use of Montelukast in asthma with comorbid allergic rhinitis patients, improved morning PEF_R significantly compared with double dose ICS group which had the same result as Claes-Goren L et al⁽¹⁴⁾.

3. Bronchiolitis and viral induced wheeze

RSV is an RNA virus that causes inflammation of the lower airway and bronchiolitis in children, especially those younger than two years old. 90% of bronchiolitis are caused by RSV infection and can present with lower respiratory airway obstruction and wheezing. In some cases there will be recurrence and turn to be asthmatic. Cysteinyl-leukotrienes are released during RSV infection and may contribute to the inflammation and variation of severity of symptoms. Bronchodilator treatment, steroid and ribavirin had no significant effectiveness.

Bigard H et al⁽¹⁵⁾ studied a randomized trial of 28 days of Montelukast in RSV-induced bronchiolitis in 130 patients age 3- 36 months. Montelukast significantly reduced lung symptoms and severe exacerbation subsequent to RSV bronchiolitis compared with placebo.

4. Chronic rhinitis symptoms

Chronic rhinitis symptoms can be caused from allergic rhinitis (positive skin prick test) and non-allergic rhinitis (negative skin prick test). The first choice of treatment in moderate to severe rhinitis symptoms is intranasal corticosteroid, but the response in non-allergic rhinitis group is less than allergic rhinitis group. At present, Montelukast has shown to be more beneficial in the non-allergic rhinitis group than intranasal corticosteroid, especially in non-allergic rhinitis with chronic hyperplastic sinusitis. In case of severe allergic rhinitis that did not respond to high dose intranasal corticosteroid, adding Montelukast to higher dose INS improved rhinitis symptom and can decrease the dose of intranasal steroid. The compliance of oral form of Montelukast is better than inhaled medication. It can have fewer side effects despite in young children, and proven to be an anti-inflammatory medication. Despite the efficacy of Montelukast is less than corticosteroid, the use in selected patient with proper condition may decrease morbidity, complications and side effect of intranasal corticosteroid, especially in young children.

Conclusion

LTRA can now be used efficiently as monotherapy in mild persistent asthma and can be added to ICS in moderate and severe persistent asthma. The advantage of Montelukast compared to ICS is that it is an orally administered drug, chewable and has no side effect in growth suppression. It can be a conventional used in asthmatic patients with comorbid allergic rhini-

tis, which is more beneficial than in asthma alone. However, it is more expensive when compared with ICS alone. However, choosing a medication for the patient must include the following consideration: compliances, efficiency, cost and side effects properly for each patient. Proper education to the patient, plan of treatment and long-term follow up, avoidance of trigger factors are major roles for the success of asthma treatment in children. Montelukast shows benefit in preventing recurrence of wheezing in post bronchiolitic children, known as viral-induced wheezing. Montelukast can be used in infants with bronchiolitis to improve quality of life and increase in symptoms free days. Any medication in a form of oral therapy is, therefore, a convenient way to administer to very young children. The use of Montelukast is less expensive than inhaled steroid alone in the control of asthma with other allergic diseases. However, Montelukast can control allergic rhinitis symptoms, and therefore this benefit will improve the quality of life of the patients with both asthma and allergic rhinitis.

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มอนติลูคาสในกุมารเวชปฏิบัติทั่วไป

จรงค์จิตร งามไพบูลย์

ปัจจุบันพบว่าเด็กที่ป่วยเป็นโรคภูมิแพ้มีจำนวนมากขึ้นทุกวัน ทั้งที่มียาดี ๆ มากมาย ยังพบว่าผู้ป่วยที่เป็นโรคภูมิแพ้มีอัตราการตายเพิ่มมากขึ้น ทั้งนี้ไม่ว่าผู้ป่วยเด็กจะป่วยเป็น Allergic rhinitis, Atopic dermatitis, Asthma ล้วนมีกลไกการเกิดโรคในลักษณะ Ig E mediated hypersensitivity ทั้งสิ้นโดยมีสาร Leukotriene (LT) เป็นตัวกลางที่ก่อให้เกิดโรค ดังนั้นการเข้ายาด้านสารนี้ในการรักษาจึงเป็นเรื่องที่น่าสนใจเป็นอย่างยิ่ง มอนติลูคาส เป็นยาชนิดรับประทานกลุ่มใหม่ที่ออกฤทธิ์ต้าน chemical mediator ที่ receptor ของ cysLT1 ที่ได้มาจาก activated mast cell คือ leukotrienes ซึ่งมีผลทำให้มี chronic inflammation ตามมา ดังนั้นยาในกลุ่มนี้จึงถือได้ว่ามีฤทธิ์เป็น anti-inflammatory effect เหมือนกัน และในปัจจุบันก็มีงานศึกษาวิจัยเกี่ยวกับยาตัวนี้มากมายในการรักษาโรคหอบหืด โรคเยื่อจมูกอักเสบจากภูมิแพ้ การหอบเนื่องจากหลอดลมฝอยอักเสบจากการติดเชื้อไวรัสและหวัดเรื้อรัง สำหรับหลักฐานที่มีผลการนำยา Montelukast มาใช้ในการรักษาในเด็กนั้น ปัจจุบันสามารถใช้เป็น monotherapy ใน mild persistent asthma ได้ผลดี และเป็นยาเสริมร่วมกับ inhaled corticosteroid ใน moderate to severe persistent asthma อย่างไรก็ตามการใช้ Montelukast สามารถลดอาการภูมิแพ้ทางจมูกได้ด้วย โดยไม่มีผลข้างเคียงเรื่องการกดการเจริญเติบโตเมื่อเทียบกับ inhaled corticosteroid รวมทั้งในกรณีที่ผู้ป่วยหอบหืด ที่มีอาการภูมิแพ้ทางจมูกร่วมด้วย การเข้ายาดังนี้จะทำให้อาการดีขึ้นทั้ง 2 อย่าง ทำให้คุณภาพชีวิตผู้ป่วยดีขึ้น