Review of montelukast use over the past 20 years and monitoring of its effects

Running title: Montelukast in wheezy children

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ABSTRACT

Montelukast is a representative leukotriene receptor antagonist that was launched 20 years ago in Korea. It is recommended as an alternative initial treatment to control asthma in children with mild persistent symptoms or as an add-on treatment to low-dose inhaled corticosteroids (ICS) in children that require additional treatment. However, in a real-world setting, many doctors and patients prefer using montelukast over ICS, even though the efficacy of montelukast is lower than that of ICS. Montelukast is considered a safe drug; however, concerns have been raised relating to adverse drug reactions, including the rare occurrence of Churg-Strauss syndrome and, although the available data are insufficient to confirm this, the possibility of increased suicidality. We found that montelukast has contributed significantly to asthma control over the past 20 years in Korea, and has been critical for reducing asthma severity, especially with regard to early wheezing and asthma control. In addition, we suggested that the effects of montelukast treatment may be monitored by the measurement of serum eosinophil-derived neurotoxin (EDN) levels.

Keywords: Wheezing, Asthma, Montelukast, Children, Eosinophil-derived neurotoxin
INTRODUCTION

The term leukotrienes (LTs) describes substances that are secreted by leukocytes and have three conjugated double bonds. Researchers have known since 1930 that the sputum of asthmatic patients contains substances that cause smooth muscle constriction.\(^1\) This substance was called the slow-reacting substance of anaphylaxis (SRS-A) as it causes the slow contraction of the smooth muscle after being released from sensitized lungs during an anaphylactic reaction.\(^2\) In the late 1970s, SRS-A was shown to be part of the LT family.\(^3\) In 1980, it was reported that both leukotrienes C\(_4\) and D\(_4\) (LTC\(_4\) and LTD\(_4\), respectively) showed remarkable contractile activity on isolated human bronchi.\(^4\) Thereafter, the number of studies on LTs as candidates for the treatment of asthma has increased. LT modifiers include LT receptor antagonists (LTRAs) and 5-lipoxygenase (5-LO) inhibitors. LTRAs include zafirlukast, montelukast, and pranlukast, and 5-LO inhibitors include zileuton. Of these, montelukast is the most widely prescribed and studied in the world. This review describes the synthesis and function of LTs and the effects and safety of montelukast, a representative LT modifier.

**Biosynthesis of LTs**

The biosynthesis of LTs begins in the cell membrane. When a variety of biological stimuli occur, phospholipids in the cell membrane are metabolized to arachidonic acid (AA) by phospholipase A2. AA is converted to prostaglandin (PG) or thromboxane by cyclooxygenase, or to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) by 5-lipoxygenase (5-LO) and 5-LO-activating protein (FLAP). 5-HPETE is then transformed into either 5-hydroxyeicosatetraenoic acid (5-HETE) or LTA\(_4\). LTA\(_4\) is either converted to LTB\(_4\) by LTA\(_4\) hydrolase or binds to reduced glutathione using LTC\(_4\) synthase to form LTC\(_4\). LTC\(_4\) is converted to LTD\(_4\) by the removal of glutamic acid by \(\gamma\)-glutamyl transpeptidase (r-GTP),
and LTD4 is converted to LTE4 by the removal of glycine by dipeptidase. LTC4, LTD4, and LTE4 are called cysteinyl LTs (cysLTs) because they contain cysteine.

**Role of LTs in the airway**

CysLTs have several effects that contribute to the pathogenesis of asthma. First, they act as potent bronchoconstrictors in humans. When the lung tissues of asthmatic patients were stimulated with specific allergens, the secretion of cysLTs increased and the amounts of cysLTs released were correlated to bronchial smooth muscle contraction.\(^5\) When LTD4 was inhaled *in vivo*, the bronchial smooth muscle contracted and lung function was decreased regardless of asthma.\(^6\) CysLTs up-regulate the expression of endothelial adhesion molecules, act as a powerful chemoattractant for eosinophils, and reduce eosinophil apoptosis, thus leading to eosinophilic inflammation.\(^7\) CysLTs also increase vascular leakage, which in turn exacerbates mucosal edema, increase mucus production and secretion by goblet cells, and decrease mucociliary clearance.\(^8-10\) Furthermore, cysLTs contribute to airway remodeling, promote the proliferation of smooth muscle cells, and increase collagen deposition in the airways (Figure 1).\(^11,12\)

CysLT receptors are classified as cysLT1 and cysLT2. Montelukast, zafirlukast, and pranlukast are selective cysLT1 antagonists. CysLT1 is expressed in macrophages, dendritic cells, eosinophils, basophils, mast cells, B cells, CD4+ T cells, hematopoietic progenitor cells, epithelial cells, airway smooth muscle cells, fibroblasts, fibrocytes, and endothelial cells. CysLT2 is expressed in macrophages, eosinophils, basophils, mast cells, epithelial cells, fibrocytes, and endothelial cells.\(^13\) Binding affinity for cysLT1 among cysLTs is the highest in LTD4, followed by LTC4 and LTE, which shows very weak binding affinity. The binding affinity for cysLT2 is similar in LTD4 and LTC4, and that of LTE4 is weak.\(^13-15\) There is no selective cysLT2 antagonist currently available. Commercialized LTRAs, such as
montelukast, pranlukast, and zafirlukast, act selectively on cysLT1, but not on cysLT2. Therefore, asthma-associated cysLT activity is thought to involve cysLT1.

**Clinical use of montelukast in children with asthma**

**Current pediatric asthma management guidelines**

The current guidelines state that low-dose inhaled corticosteroids (ICS) may be used primarily in children of all ages when maintenance therapy is needed, and that LTRAs should be administered as an alternative treatment. If step-up treatment is required, prescription of moderate-dose ICS or LTRAs in combination with low-dose ICS is recommended for children aged <5 years. For children aged >6 years, the use of low-dose ICS in combination with long-acting beta-2 agonists (LABA) is recommended, and high-dose ICS or low-dose ICS with LTRAs are recommended as alternative treatments.\(^{16,17}\)

**Comparison with ICSs**

A Cochrane review, which analyzed 19 pediatric randomized controlled trials (RCTs) to compare the efficacy of montelukast to that of ICS, revealed the superior efficacy of ICS.\(^{18}\)

A meta-analysis of RCTs in preschoolers with asthma or recurrent wheezing also reported that the daily use of ICS was more effective than montelukast treatment.\(^{19}\) However, several studies showed different outcomes in real-life environments as the actual effects of medication are determined both by the efficacy of the medication and patient compliance. Ducharme et al.\(^{20}\) examined the real-life effectiveness of montelukast versus that of ICS in children with mild or moderate asthma. Physicians prescribed medication for 62% of the follow-up period if they prescribed ICS, and for 97% if montelukast was prescribed. Patients purchased 51% versus 74% of the prescribed ICS and montelukast at pharmacies, respectively. As a result, children who were prescribed ICS used the medication for 24% of
the follow-up period and those who were prescribed montelukast used the medication for 38% of the follow-up period. There was no difference in the rates of oral corticosteroid use or emergency room visits between the two groups, but ICS prescription groups were the more frequently admitted and more frequently used rescue beta-2 agonists.\(^\text{20}\) According to a study analyzing the Korean National Health Insurance claim database from 2010 to 2014, LTRAs including montelukast were the most prescribed in children of all ages with asthma. The rate of ICS prescription for asthmatic patients aged ≥6 years was <15%.\(^\text{21}\) These results suggest that Korean pediatricians prefer to prescribe montelukast rather than ICS. In a recent survey of 1,838 pediatric patients currently receiving treatment for asthma in Korea and their parents, 38% of patients receiving inhaled treatment and 50% of those receiving LTRAs were taking the treatment as prescribed. Furthermore, 70% of LTRA users felt that their treatment modality was easy to use compared to only 34% of inhaler users.\(^\text{22}\)

A randomized study comparing responses to fluticasone inhaler and montelukast treatment in school-aged children with mild to moderate asthma defined a response as a ≥7.5% improvement in forced expiratory volume in 1 s (FEV1), and showed that 5% of the children responded to montelukast only, 23% responded to fluticasone only, 17% responded to both medications, and 55% did not respond to either medication. Predictors of good response to fluticasone only were lower pulmonary function and provocative concentration causing a 20% drop in FEV1 (PC20), and higher FeNO levels, total eosinophil counts, serum eosinophil cationic protein (ECP), and total immunoglobulin E (IgE). Conversely, predictors of good response to montelukast only were lower age and short duration of asthma.\(^\text{23}\)

In summary, although the efficacy of montelukast is inferior to that of ICSs, and guidelines for asthma management recommend that ICSs should be prescribed primarily when starting maintenance therapy, both physicians and patients prefer montelukast to ICSs. In addition, some patients respond better to montelukast than to ICS, but additional studies are needed to
determine which patients will respond better.

**Preschool children with asthma or recurrent wheezing**

There are no specific tools or biomarkers available to diagnose asthma in preschool children. Therefore, it is important for physicians to recognize the various patterns of recurrent wheezing in preschool children. The proposed phenotypes of recurrent wheezing in early childhood are as follows: transient wheezing, nonatopic wheezing, persistent asthma, and severe intermittent wheezing.\(^{24,25}\) This classification is helpful in understanding childhood wheezing, but is difficult to use clinically. Wheezing may be classified as an “episodic (viral) wheeze” (EVW) or “multiple-trigger wheeze” (MTW).\(^{26}\) An EVW is defined as wheezing during discrete time periods, often in association with the clinical evidence of a viral cold, with an absence of wheezing between episodes. An MTW is defined as wheezing that shows discrete exacerbations, but also symptoms between episodes.

Recently, a meta-analysis of the effects of montelukast treatment for the prevention of post-bronchiolitis wheezing was reported.\(^{27}\) The authors concluded that montelukast reduced the frequency of recurrent wheezing but did not reduce the incidence of recurrent wheezing, the use of corticosteroids, or the number of symptom-free days in post-bronchiolitis infants; therefore, it was not appropriate for clinical use. However, in a randomized control study of post-bronchiolitis treated with montelukast for three months and followed up for 12 months, the serum eosinophil-derived neurotoxin (EDN) levels were significantly decreased and cumulative recurrent wheezing episodes were significantly lowered in the montelukast-treated group.\(^{28}\)

A Cochrane review of the effects of LTRA against EVW in preschool children reported that LTRA maintenance or intermittent therapy did not reduce the number of children experiencing one or more episodes requiring rescue medicine, emergency room visit, and
hospital admission. However, the authors suggested that certain subgroups may respond to LTRA, as children with EVW did not show homogeneous phenotypes; they should be prescribed montelukast as a therapeutic trial and should continue maintenance therapy if they respond well. The European Respiratory Society (ERS) recommended that in children with EVW, montelukast should be the first choice for daily maintenance therapy, and in children with MTW, ICSs should be the first choice for maintenance therapy. However, the ERS highlighted that it is difficult to distinguish EVW from MTW in some children. A recent meta-analysis of the effects of montelukast against both EVW and MTW in preschool children reported that the use of montelukast in preschool children with recurrent wheezing was not effective. The authors suggested that further studies should be conducted to investigate how to easily identify montelukast responders in clinical settings.

EDN may be a useful biomarker for the treatment and monitoring of pre-school children with asthma or recurrent wheezing. EDN is one of four major proteins secreted by activated eosinophils together with ECP, major basic protein (MBP), and eosinophil peroxidase (EPO). Unlike the other three, EDN has an isoelectronic point of 8.3, which is close to neutrality, and it is therefore possible to measure accurately and reproducibly in the blood. In a previous study, we compared the concentrations of serum EDN to asthma symptom scores in pre-school children. Serum EDN levels were the highest in children with acute asthma, followed by those with stable asthma, and those in the control group, and the differences amongst the three groups were significant. Another study suggested that serum EDN levels three months after respiratory syncytial virus (RSV) bronchiolitis were predictive of recurrent wheezing within 12 months. The serum EDN concentration cut-off value for predicting wheezing recurrence was 53 ng/mL (positive predictive value: 57%, negative predictive value: 76%, sensitivity: 72%, and specificity: 62%). The normal range of serum EDN concentration was 13–45 ng/mL. Another recent study compared the effects of montelukast and 0.5 mg
budesonide inhalation suspension (BIS) therapy for 12 weeks in symptomatic preschool children with asthma and serum EDN levels ≥53 ng/mL.\(^{37}\) During the study period, asthma control days increased in both groups, and there was no significant difference between the two groups. However, serum EDN levels were significantly decreased only in the montelukast group. Therefore, based on several years of EDN-related research, we recommend starting maintenance therapy with montelukast when the EDN concentration level is ≥ 53 ng/mL (1 SD of normal) and stopping when the EDN concentration level decreases below 45 ng/mL (Figure 2).

Current clinical practice guidelines recommended controller therapy for children experiencing daytime asthma symptoms more than once a week, activity limitation, who require the use of a reliever more than once a week, or have any nighttime symptoms.\(^{16}\) However, a recent study compared the efficacy of montelukast maintenance therapy and as-needed β2-agonist therapy for 48 weeks in preschool children experiencing asthma symptoms more than once a month but less than once a week.\(^{38}\) During the study, 28% of the montelukast group and 50% of the no-controller group experienced asthma exacerbation and 21% and 41% of the children, respectively, received increased treatment. Therefore, montelukast should be considered for use as a maintenance therapy in preschool children with intermittent asthma.

The efficacy of LTRAs combined with antihistamines is often mentioned in clinical journals and guidelines. The combination of montelukast and 2nd generation antihistamines may protect against seasonal decrease in lung function in patients with allergic rhinitis. Furthermore, LTRAs may be more effective in the treatment of allergic rhinitis when combined with antihistamines as both agents have a different efficacy range. Recently, one such compound was developed and marketed for children in Korea.\(^{39}\)
Safety profile

The most commonly reported clinical adverse events of montelukast treatment were fever, upper respiratory infection, and asthma exacerbation. However, montelukast is considered to be a safe drug because the incidence of adverse drug reactions (ADRs) was similar to that in the control group.\textsuperscript{40}

Major concerns related to montelukast-associated ADRs were the occurrence of Churg-Strauss syndrome (CSS) and the possible association between LTRA and suicidality. A case-crossover study of 78 patients with CSS reported that the use of montelukast was associated with a 4.5-fold increased risk of CSS onset within three months.\textsuperscript{41} CSS, also known as eosinophilic granulomatosis with polyangiitis (EGPA), is a rare autoimmune disorder that causes vasculitis in patients with a history of asthma or allergic rhinitis. Treatment for CSS includes glucocorticoids (such as prednisolone) and other immunosuppressive drugs. Therefore, montelukast is simply a confounding factor and the withdrawal of steroid use may be associated with the development of CSS symptoms.

In 2008, the US Food and Drug Administration (FDA) issued a warning about the possible association between the use of montelukast and suicidality. A recent review on this issue reported that several ecological studies concluded that the use of montelukast was not associated with suicidal ideation or attempts at the population level. However, the authors noted that this association did not completely disappear at the individual level.\textsuperscript{42}

CONCLUSION

The efficacy of montelukast on pediatric asthma is inferior to that of ICSs. Nonetheless, montelukast presents several advantages. First, patients using ICS must use the correct technique for inhalation, but no special skills are required to administer montelukast. Second, both the patients and the prescribing physicians prefer to use a drug that is administered only
once a day. Third, there is no impact on growth, unlike the use of ICS, which can potentially impair a child’s growth.\textsuperscript{43\textsuperscript{)}

Montelukast maintenance therapy is primarily recommended for asthmatic children who experience symptoms more than once a month but less than once a week and is recommended as an alternative method for children with step 2 asthma.

Serum EDN can be used as a biomarker to monitor the effectiveness of pediatric asthma treatment. We recommend starting maintenance therapy with montelukast when the EDN level is $\geq 53$ ng/mL and stopping when the EDN level decreases below 45 ng/mL. However, additional studies are needed to determine the validity of these recommendations.
REFERENCES

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**Figure legends**

Fig. 1. Biosynthesis and role of Leukotrienes. 5-LO, 5-lipoxygenase; FLAP, 5-LO-activating protein; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; 5-HETE, 5-hydroxyeicosatetraenoic acid; LT, leukotriene; γ-GTP, γ-glutamyl transpeptidase.

Fig. 2. Monitoring of leukotrien receptor antagonist (LTRA) effects
### Table 1 Clinical effects of montelukast in preschool children

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Clinical effects of montelukast</th>
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<tbody>
<tr>
<td><strong>Wheeze</strong></td>
<td></td>
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<tr>
<td>Episodic viral wheeze</td>
<td>Decrease in wheezing frequency after RSV infection. No short acting effects on reducing wheezing episodes requiring rescue medicine, ER visit, and hospital admission. Recommended as a therapeutic trial</td>
</tr>
<tr>
<td>Multiple trigger wheeze</td>
<td>Montelukast responder’ phenotype exists. Studying how to easily identify these phenotypes</td>
</tr>
<tr>
<td></td>
<td>Recommended as an alternative treatment of low-dose inhalation corticosteroids (ICS)</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
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<tr>
<td>Intermittent</td>
<td>Effective on reducing asthma exacerbation</td>
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<tr>
<td></td>
<td>Recommended as an additional treatment of short-acting beta agonist</td>
</tr>
<tr>
<td>Persistent</td>
<td>Effective on reducing serum EDN concentrations.</td>
</tr>
<tr>
<td></td>
<td>Less effective than daily ICS for improving asthma symptoms and preventing exacerbation</td>
</tr>
<tr>
<td></td>
<td>Recommended as an alternative treatment of low-dose ICS</td>
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</tbody>
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Airway smooth muscle
- Contraction ↑
- Proliferation ↑
- Hyperresponsiveness

Mucus gland
- Secretion ↑
- Metaplasia

Eosinophil
- Influx ↑
- Apoptosis ↓

Blood vessel
- Edema ↑
- Leakage ↑

Airway epithelium
- Hypertrophy ↑
- Mucociliary clearance ↓

**Phospholipase A2**

**Arachidonic acid**

**5-LO/FLAP**

**Cyclooxygenase (COX)**

5-HPETE → 5-HETE

LTA4 hydrolase

LTA4synthase

LTA4 hydrolase

LTC4 synthase

LTC4

\( \gamma \)-GTP

LTD4

Dipeptidase

LTE4

**Cysteinyl leukotrienes**

Leukotriene Receptor Antagonist

Leukotriene receptor

(eosinophil, smooth muscle cell, etc)