Is montelukast effective and well tolerated in the management of asthma in young children?

Part A: Evidence-based answer and summary

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Montelukast is a leukotriene-receptor antagonist (LTRA), a class of drugs that became available in the 1990s for the treatment of asthma. LTRAs are one of the few new drugs that have been introduced in asthma therapy since the advent of inhaled corticosteroids (ICS) in the early 1970s. LTRAs have both anti-inflammatory and bronchodilator effects because the cysteinyl leukotrienes whose effects they block mediate both inflammation and bronchoconstriction (1).

Montelukast is an attractive drug for several reasons. Oral preparations are easier to administer in young children than inhaled medications. Once-daily dosing is practical and encourages compliance. The LTRAs have a wide therapeutic window, with low toxicity at therapeutic concentrations. Even in overdose, montelukast appears safe, although data are limited at present (2). This is in contrast with other orally administered antiasthma medications, such as steroids, theophyllines or beta$_2$-agonists.

There are many trials in adults and older children demonstrating that montelukast is beneficial and well tolerated, with relatively few trials in infants and younger children. Discussions on montelukast in young children will be heavily influenced by the few trials that have been conducted in this age group, but will also include information that can be reasonably extrapolated from trials in older children. Most of the early evidence for the benefits of montelukast in childhood asthma came from large, randomized, placebo-controlled trials of children sponsored by the drug manufacturer (3-6). More recently, there have been randomized, controlled trials comparing montelukast with ICS (7-9).

The pathophysiology of childhood wheeze changes with age. In many asthma trials, children of different ages are dealt with separately. Montelukast has been investigated in school-aged children (six to 14 years of age) with persistent or intermittent symptoms (5), preschool children (two to five years of age) with persistent (4) or intermittent asthma (3), and in infants (six to 24 months of age) with 'asthma-like symptoms' (6). These studies are typically well designed and executed. There are some similarities among the studies. For example, in most studies, children are allowed to continue on ICS or sodium cromoglycate if this had been established before recruitment. The studies have slightly differing methodologies, lengths of treatment and outcome measures. Some of the studies are primarily aimed at investigating the safety and tolerability of montelukast in children with measures of efficacy as secondary outcomes.

Montelukast has been assessed in children two to five years of age with persistent or with intermittent symptoms. Knorr et al (4) randomly assigned 689 preschool children with persistent asthma symptoms to montelukast or placebo in addition to their usual inhaled treatment (which could include inhaled beta$_2$-agonists, ICS or sodium cromoglycate) for 12 weeks. Montelukast produced a small but significant reduction in several measures of asthma control, including percentage of days with daytime asthma symptoms (reduced from 64% to 59% [P=0.012]). Similarly, Bisgaard et al (3) examined the influence of montelukast compared with placebo in 549 preschool children with intermittent asthma symptoms over a period of 48 weeks. Asthma exacerbations were reduced from an average of 2.34 episodes per year in the placebo group to 1.60 episodes per year in the treatment group (P<0.001). In a six-week study in 359 infants between six and 24 months of age with 'asthma-like symptoms', montelukast has been shown to be safe and well tolerated (6). It did not affect secondary measures of asthma control. Subgroup analyses of these studies were unable to predict which children in particular would benefit from montelukast (10). Montelukast has also been shown to reduce the symptoms of cough and wheeze following bronchiolitis in infancy (11). Montelukast may be useful in the particular

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instance where exercise-induced symptoms predominate, and has been shown to help in children as young as six years of age (12). A history of exercise-induced symptoms may be more difficult to elicit in younger children.

In all of these studies, montelukast has appeared to be safe and well tolerated, with the incidence of side effects similar in the treatment group and control groups taking placebo or ICS. However, these studies were powered only to detect frequent side effects (the study by Knorr et al [4] was powered to detect adverse effects with an incidence of 7.8% in the treatment group). Surveillance of montelukast in clinical practice would also suggest it is a safe drug. There are reports of idiosyncratic effects such as urticaria, erythema nodosum, pemphigus, bleeding and Henoch-Schonlein purpura, and other more general cautions are included in standard prescribing advice. Other LTRAs may induce hepatic dysfunction. This appears to be very rare with montelukast, although it has been reported (13).

In conclusion, montelukast is a safe drug with modest benefits in the treatment of asthma in young children. The current recommendation in most practice guidelines that montelukast should be considered as an add-on therapy to ICS and inhaled beta$_2$-agonists in children with persistent asthma appears reasonable. Montelukast may also be considered where ICS are impractical. In the particular situation of young children who suffer symptoms only intermittently in response to upper respiratory tract infections, montelukast has been shown to be beneficial where the evidence over ICS remains conflicting.

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Part B: Clinical commentary

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Asthma in preschool children is a particularly troublesome problem for the clinician. This age group is susceptible to multiple virus infections, often in association with daycare, resulting in frequent exacerbations. In addition, inhaled medication, effective in older children, can be difficult to deliver to the toddler. Montelukast, therefore, is a welcome addition to the asthma treatment arsenal. It can be given by chewable tablet or sprinkled granules mixed with food.

Montelukast has a very narrow site of action in comparison to the broad anti-inflammatory action of the commonly used inhaled corticosteroids. As one of the leukotriene-receptor antagonists, it blocks the action of cysteinyl leukotrienes, which catalyze the inflammatory cascade from eosinophils, mast cells and alveolar macrophages (1). This reduces the main characteristics of asthma, such as airflow obstruction, mucus hypersecretion, mucosal edema and desquamation, bronchoconstriction, bronchial hyperresponsiveness and eosinophil accumulation.

The papers chosen (2-4) investigate whether montelukast is a useful and safe medication for the younger patient with asthma. It should be noted at the outset that the drug manufacturer sponsored all of these studies. Two studies looked at the preschool age group (two to five years of age), comparing montelukast with placebo (2,3). Both studies selected young patients with intermittent asthma triggered by colds. Some of the patients in the study were on inhaled steroids (29% for Knorr et al [3] to 45% for Bisgaard et al [2]). This is important because additive asthma control would be beneficial. Both studies were multinational, multicentre and well designed, although there were no details about allocation concealment. Patients had a run-in period and then were treated in a randomized, double-blind fashion. Knorr et al (3) followed patients for three months, and Bisgaard et al (2) followed patients for almost one year. In both studies, the conclusions were essentially the same: decreased asthma exacerbations and consequently, fewer requirements for 'rescue' treatment. The longer duration study quantified this as a reduction from 2.34 exacerbation episodes to 1.60 per year (2). This was a statistically significant result, but was it a clinically important improvement to justify a daily medication? The investigators commented that the benefit was greatest during the autumn and winter, suggesting, therefore, that patients may only require treatment for part of the year.

The other study (4) posed a different question in a different group of patients: does montelukast have serious adverse effects in infants and toddlers (six to 24 months of age)? This study again examined patients with physician-diagnosed asthma or at least three 'asthma-like' episodes. Approximately one-half of the patients were already on inhaled corticosteroids. Patients were randomly assigned into montelukast or placebo for a six-week period. The study was powered to detect an adverse effect rate of 19.4% in the montelukast group and 1% in the placebo arm. The patients were examined every two weeks, and all effects were recorded. There were no differences in adverse effects in each group. The conclusion was that the adverse effect frequency was similar in both the placebo and drug groups. The investigators also looked for a reduction in asthma symptoms, but there was no difference between montelukast and placebo groups. It is likely that the study was not of sufficient duration to fully assess these outcomes.

How do these studies help us in the care of patients? This medication has several advantages. It can be taken orally and this may improve compliance (5,6). It is not a steroid, which may appeal to some parents who are concerned about potential side effects. It appears to be safe and well-tolerated in our youngest patients. Its disadvantages are that it is generally weaker than 400 mg of inhaled beclomethasone (or equivalent), and that patients are more likely to suffer a flare up when on this medication alone (7). In very young patients (under two years of age), montelukast may be only modestly beneficial. In summary, montelukast

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would appear to be useful in reducing asthma exacerbations by approximately one-third. This drug is recommended as the next step after inhaled steroids in most guidelines (8,9). It appears to be useful for the preschool age group and when there is coexisting allergic rhinitis (10). Montelukast may also help reduce symptoms when used as a short course in intermittent asthma, but this remains to be confirmed in other studies (11).

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