

An evaluation of montelukast for paediatric asthma

Montelukast is a leukotriene receptor antagonist licensed for the prophylaxis of asthma in children. Here, the North Central London Formulary and Medicines Management Group assess the efficacy of montelukast in addition to, and as an alternative to inhaled corticosteroids.

Asthma guidelines from the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidance Network (SIGN) were reviewed and updated last year.⁴ Montelukast is now recommended:

- In children under the age of five who cannot use an inhaled corticosteroid (ICS)
- As add-on therapy to an ICS in children under five whose asthma is poorly controlled
- As add-on therapy to an ICS and a long acting beta₂-receptor agonist (LABA) in children aged five to 12 years whose asthma is poorly controlled

This review reports on the efficacy of montelukast in addition to ICSs, and as an alternative to ICSs in both persistent and intermittent asthma.

Efficacy

Addition to an ICS: persistent asthma

Simons *et al*⁵ conducted a multicentre, randomised, double-blinded, cross-over study of 279 children aged six to 14 years with corticosteroid-dependent, persistent asthma. The study compared montelukast 5mg/day and inhaled budesonide (400µg/



Inhaled therapy can be difficult for younger children

day) versus placebo and inhaled budesonide. Prior treatment (≤6 weeks) included the use of budesonide (200–800µg/day or equivalent). The study ran for 12 weeks and was statistically powered to 90% (n=200) to detect a 4.4% difference in forced expiratory volume in one second (FEV₁).

The primary endpoint was percentage change in FEV₁ from baseline, where the authors reported a modest benefit over placebo; montelukast +6.0%, placebo +4.1%, absolute benefit increase (ABI) +1.9% (p=0.01). However, these data are derived from a per-protocol analysis. More

importantly, the primary intention-to-treat analysis (251 patients, 90% follow-up) yielded no significant difference between montelukast and placebo in terms of FEV₁ (montelukast +4.6%, placebo +3.3%; ABI +1.3%; p=0.62). No absolute values of FEV₁ were reported in the manuscript.

It was not stated whether the secondary efficacy endpoints were based on the per-protocol or intention-to-treat population and they are therefore difficult to interpret.

Johnston *et al*⁶ conducted a double-blind, randomised, placebo-controlled trial to investigate the impact of montelukast on asthma symptom reduction (in days) and unscheduled physician visits, when added to usual asthma therapy in 194 children aged two to 14 years (montelukast n=98, placebo n=96). Based on the results of a pilot study, a 40% reduction in the number of days with worse asthma symptoms was expected in the montelukast group (primary endpoint), defined as increased cough, wheeze, or trouble breathing, or worsening of breathing symptoms severe enough to see a physician.

At baseline, over 90% of patients had been prescribed an ICS, with 30% in each group prescribed a combination product (ICS and LABA). Overall, 4.4% (3.9% vs 8.3%; p<0.02) fewer children taking montelukast experienced a worsening of asthma symptoms. In the montelukast group fewer patients required unscheduled visits to their physician (4 vs 18, p=0.11), and they were less likely to report using a short acting β₂-receptor agonist during the study (average 6.8 days of using rescue medication vs 9.4 days; p=0.05) although these results failed to meet statistical significance. The mean number of days of ICS use was similar in both groups.

Since the study enrolled a small number of patients over a short duration of time (45 days), the clinical significance of the results is uncertain.

Background

Asthma is a chronic disease, prevalent in childhood. Cysteinyl leukotrienes are potent mediators of airway inflammation and are believed to contribute significantly to the pathophysiology of asthma.¹

Leukotriene receptor antagonists (LTRAs) may reduce bronchoconstriction and mucous secretion, with a subsequent reduction in inflammation.² Montelukast (Singulair; MSD) is an oral LTRA licensed for asthma prophylaxis in children over the

age of six months, and for the symptomatic relief of seasonal allergic rhinitis in asthmatic children aged over 15 years.

The authors have previously reviewed the evidence for the use of montelukast in the paediatric population, but were unable to provide firm recommendations due to limited evidence.³ Several studies on the use of montelukast in children with asthma have been published since this review and are summarised in this article.

Alternative to an ICS: persistent asthma

Garcia *et al*⁷ conducted a 12-month, multicentre, randomised, double-blind, non-inferiority trial to determine the effect of montelukast 5mg/day (n=495), compared with 100µg twice-daily inhaled fluticasone (n=499) in patients aged six to 14 years old with mild, persistent asthma. The primary endpoint was the percentage of rescue free days (RFDs) compared with baseline over the 12 month period. RFDs were defined as days without the use of rescue medication or asthma-related resources (intention-to-treat population). At 12 months, the mean percentage of RFDs was 84% in the montelukast group and 86.7% in the fluticasone group (baseline 64%).

Although the difference fell within the non-inferiority margin (≤7%), the proportion of patients requiring systemic corticosteroids and experiencing asthma attacks was greater in the montelukast group. Secondary endpoint measures including FEV₁ (0.9% vs 2.8%; p=0.004), and days with β₂-receptor agonist use (15.4% vs 12.8%; p=0.003) showed greater improvement in the fluticasone group.

The proportion of patients requiring additional rescue medication, excluding short-acting β₂-receptor agonists, was 20.7% vs 13.5%; relative risk 1.56 (95% CI, 1.17 to 2.06) in favour of fluticasone. The majority of patients using rescue medication (17.8% vs 10.5%) used systemic corticosteroids. Of these, 61.2% in the montelukast group and 55.8% in the fluticasone group required only one course over the study period. The proportion of patients who experienced an asthma attack was 32.2% vs 25.6%; relative risk 1.26 (95% CI, 1.04 to 1.52) in favour of fluticasone.

Ducharme and di Salvo⁸ conducted a review (for the Cochrane Collaboration) to

Drug appraisal articles

University College London Hospitals NHS Foundation Trust, Royal Free Hampstead NHS Trust and The Whittington Hospital NHS Trust operate a centralised medication review scheme for assessing formulary applications to their Use of Medicine and Drugs and Therapeutics Committees. A review of selected formulary applications will be published regularly in *The British Journal of Clinical Pharmacy*.

Drug, strength and preparation	Usual dose	No. of doses	Unit cost	Cost per day
Fluticasone 50µg/puff MDI	2 puffs twice each day	120 doses	£5.44	£0.18
Beclometasone 100µg/puff MDI	2 puffs twice each day	200 doses	£15.16	£0.30
Montelukast 4mg/5mg tablet	1 tablet daily	28 tablets	£25.69	£0.92

Figure 1: Relative cost of montelukast and ICSs (BNF 57, March 2009)

compare the safety and efficacy of LTRAs with ICSs and to determine the dose-equivalence of LTRAs to a daily dose of ICS. Of the 27 trials that met the inclusion criteria, 13 were of high methodological quality and 20 are published in full-text. All trials pertained to patients with mild to moderate persistent asthma. Only three trials focused on children and adolescents, and the trial duration varied from four to 37 weeks. In most trials, the daily dose of ICS was 400µg/day of beclometasone dipropionate or equivalent.

Patients treated with a LTRA were 65% more likely to suffer an exacerbation requiring systemic steroids (relative risk 1.65; 95% CI, 1.36 to 2.0). A total of 26 (95% CI, 17 to 47) patients must be treated with a LTRA instead of an ICS to cause one extra exacerbation.

Significant differences favouring ICSs were noted in the secondary outcomes where the improvement in FEV₁ reached 130mL (13 trials, 95% CI, 50 to 140mL).

Other significant benefits of ICSs were seen for symptoms, nocturnal awakenings, rescue medication use, symptom-free days, and quality of life. LTRA therapy was associated with a 160% increased risk of withdrawals due to poor asthma control. A total of 29 (95% CI, 20 to 48) patients must be treated with a LTRA instead of an ICS to cause one extra withdrawal due to poor control. No significant difference in side effects was noted between the two treatment groups. The authors concluded that ICSs at a dose of 400µg/day of beclometasone dipropionate or equivalent are more effective than a LTRA given in the usual licensed doses.

Alternative to an ICS: intermittent asthma

A multicentre, double-blind, parallel-group, randomised study by Bisgaard *et al*⁹ was designed to compare the clinical effect of continuous oral montelukast 4mg/day (n=265) with placebo (n=257) in children aged two to five years with intermittent asthma. The treatment period was 48 weeks and the primary endpoint was the number of asthma exacerbation

episodes (intention-to-treat population).

At baseline, 85% of subjects had asthma symptoms no more than twice per week during the month before the study, and the proportion of patients with asthma episodes was significantly lower in the montelukast group (45%) compared with placebo (56%; p=0.008). Although montelukast reduced asthma exacerbation episodes per year compared with placebo (1.60, 95% CI, 1.35 to 1.88 vs 2.34, 95% CI, 1.97 to 2.79; p≤0.001), the absolute difference appears small (less than one episode per year).

Another multicentre, double-blind, randomised, placebo-controlled study by Robertson *et al*¹⁰ was designed to compare the clinical effect of intermittent, daily, oral montelukast (n=97) with placebo (n=105) in children aged two to 14 years with intermittent asthma, where the primary endpoint was the number of total unscheduled 'acute healthcare resource utilisations' (HRUs) related to asthma. Subjects in the montelukast group received either 4mg/day (if under six years old) or 5mg/day (if six years or older). Parents or caregivers were instructed to start treatment at the onset of asthma symptoms or the first sign of an upper respiratory tract infection. They were told to give the drug once daily for a minimum of seven days (or until symptoms had resolved for 48 hours), for up to a maximum of 20 days. A maximum of five episodes requiring treatment within the 12 month study period was permitted.

There were 163 HRUs in the montelukast group and 228 in the placebo group over 307 and 284 days, respectively, representing 29% fewer HRUs in the montelukast group. The mean duration of all episodes was 6.5 days for the montelukast group and seven days for the placebo group (p=0.30). Although total symptom scores for all episodes were significantly lower in the montelukast group, they were not significantly lower for the median number of puffs of β₂-receptor agonist used per episode, or oral steroid use.

Safety

In the study by Garcia *et al*,⁷ montelukast and fluticasone were equally well tolerated with no significant differences in the number of adverse effects. Most commonly reported adverse effects were headache and worsening of asthma symptoms.

Growth The absolute difference in the overall growth rate averaged over the 12 month period of the Garcia *et al* study was not significant between the fluticasone and montelukast group (-0.37cm/year; p=0.18). Two articles published in 2000 (Agertoft and Pedersen,¹¹ and The Childhood Asthma Management Program Research Group¹²) report on growth among children with asthma who were treated (prospectively) for many years with inhaled budesonide at a dose of 400µg/day. Both report a reduction of about 20% in growth rate during the first year of treatment. However, growth rate subsequently recovered and the children ultimately reached, or were expected to reach, a normal adult height.

Suppression of adrenal cortex with ICS:

A 36 month study by Bacharier *et al*¹³ reviewed the long-term effect on the hypothalamic pituitary adrenal axis of inhaled budesonide 400µg/day, inhaled nedocromil 16mg/day, or placebo, in pre-pubertal children with mild-to-moderate asthma. No differences in serum cortisol levels were observed between the groups following adrenocorticotropic hormone stimulation. Cumulative ICS exposure did not influence serum cortisol response to adrenocorticotropic hormone or urinary free cortisol excretion at 36 months.

Cost and convenience

Figure 1 (p176) lists the relative costs of the two most common ICS preparations compared with montelukast. The associated costs of rescue medicines have not been considered.

For some younger patients, there is a demonstrable difficulty in using and maintaining compliant use of metered dose inhalers even with the addition of spacer devices. A chewable tablet is an advantage.

Conclusion

Current data suggests that montelukast may be marginally superior to placebo, but inferior to ICSs for treating childhood asthma. The use of an ICS should

therefore remain the mainstay of asthma management. For children, the theoretical corticosteroid-sparing effect of LTRAs is appealing but has not been demonstrated. Indeed, there are data to show that patients may actually require more systemic steroids as rescue medication when taking montelukast.

The use of high dose ICSs and/or oral therapy is of particular concern in pre-pubertal children due to their known adverse-effect profile (growth retardation and adrenal insufficiency). However, current data does not appear to confirm any significant short- or long-term effects with inhaled therapy.

Although the use of a spacer, Handihaler or breath-actuated device should assist in overcoming many dexterity difficulties associated with the use of an inhaler, oral administration of LTRAs provides a significant advantage for children.

The evidence to support the use of LTRAs in the management of paediatric asthma was previously insufficient to allow firm conclusions to be drawn, because much of the rationale to support their use in children appeared to be extrapolated from adult research. The current body of evidence suggests some efficacy, however montelukast remains inferior to an ICS. Although previously recommended in national guidelines, the specific niche indications suggested in the updated joint BTS/SIGN guidelines are now justified.

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