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Clinical Evidence with Montelukast in the Management of Chronic Childhood Asthma

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Abstract

Objective: The aim of this article is to review data on the efficacy and safety of montelukast in the treatment of children with asthma.

Methodology: Available published literature, including published abstracts, is reviewed.

Results: In patients aged 6 to 14 years with asthma (n = 27), montelukast 5mg demonstrated a significant decrease in exercise-induced bronchoconstriction 20 to 24 hours postdose after 2 days of treatment. For children with chronic asthma, only one study of the regular use of a leukotriene receptor antagonist has been published. The efficacy and safety of montelukast in children aged 6 to 14 years with asthma (n = 336) were studied during an 8-week, double-blind, placebo-controlled trial. There was a significantly greater improvement in forced expiratory volume in 1 second (FEV_1) from baseline for the montelukast group (8.23%) compared with the placebo group (3.58%). There was a significant decrease in the use of a β-agonist for symptom relief, as well as in the percentage of days and percentage of patients with asthma exacerbations. An asthma specific quality-of-life (QOL) questionnaire revealed a significant overall improvement in QOL and a significant improvement in the QOL domains for symptoms, activity and emotions in montelukast recipients. There was no significant difference between montelukast and placebo recipients in the frequency of adverse events, with the exception of allergic rhinitis, which was more prevalent in the placebo group. An open label follow-up of patients from the above study was undertaken. The effect of montelukast on FEV_1 was consistent for up to 1.4 years, with the increase in FEV_1 being not significantly different from that in a small control group treated with inhaled beclomethasone dipropionate. QOL remained significantly improved during the open treatment period.

Conclusions: Montelukast appears effective and safe for the treatment of children with asthma.

Leukotrienes (LTs) are important proinflammatory biochemical mediators in asthma, and are capable of inducing bronchoconstriction, mucous hypersecretion, and increased airway vascular permeability resulting in airway wall oedema.[1-6] Recent data suggest that LTD_4 induces an insulin-like growth factor binding protein protease (MMP-1), which may play an important role in airway remodelling.[7] Cysteinyl-LTs appear to play an important role in airway changes following

allergen challenge[8,9] and exercise.[10,11] After severe, acute exacerbations of asthma in children, increases in LT levels persisted for up to one month.[12]

Methodology

The published literature on LT receptor antagonists for the treatment of children with asthma was reviewed by means of a systematic computerised citation search using Medline and a nonsystematic review of the asthma literature until September 1999. Published abstracts were also reviewed.

Discussion

When considering the clinical evidence for the use of montelukast in managing asthma in children, it is essential to ask, 'What outcomes are important?' Physicians, as well as patients and their families, have two major concerns when they consider using any new medication: 'Is it effective?' and 'Is it safe?'

The pharmacological activity of the cysteinyl-LT receptor antagonists has been assessed in laboratory-based studies, primarily in adults. In particular, LT receptor antagonists inhibit bronchoconstriction induced by inhaled LTD_4,[13,14] and appear important for the control of symptoms in aspirin-sensitive asthmatic patients.[15,16] Given the importance of allergen sensitisation in the epidemiology of asthma and in most children with asthma, it is important that LT modifiers (receptor antagonists and lipoxygenase inhibitors) inhibit both the early and late phase of allergen-induced bronchoconstriction.[17]

One aspect of particular importance to children with asthma is the ability of LT receptor antagonists to prevent exercise-induced bronchoconstriction (EIB). Most children with asthma have some degree of EIB, and physical activity is common in children as part of their everyday life.[18,19] EIB is often not recognised by children, parents and physicians.[20] Children may avoid exercise, particularly competitive activities, because of recognised or unrecognised EIB.[20] This may occur consciously or subconsciously and may have an important impact on the child's quality of life (QOL).

Initial studies in adults demonstrated the ability of LT receptor antagonists to protect against EIB.[21,22] There has been one published study of the efficacy of montelukast for the treatment of EIB in children with asthma.[23] In this crossover study in 27 patients aged 6 to 14 years, montelukast 5 mg/day significantly decreased EIB after 2 days of treatment. At the end of the dosage interval (i.e. 20 to 24 hours after the second dose), montelukast significantly decreased the area under the curve for forced expiratory volume in 1 second (FEV_1) from 0 to 60 minutes following exercise by approximately 59% (265 *vs* 590% · min for montelukast and placebo, respectively). Montelukast significantly blunted the maximal fall in FEV_1 (18 *vs* 26% for the placebo group) [fig. 1]. Studies to assess the effect of montelukast on EIB at earlier time periods after drug administration have not been conducted.

The degree of protection against EIB provided by montelukast 20 to 24 hours postdose appears comparable to that demonstrated with sodium cromoglycate and nedocromil at 20 minutes post-treatment. However, the effect of both sodium cromoglycate and nedocromil is no longer present at approximately 2 hours post-treatment.[24] In-

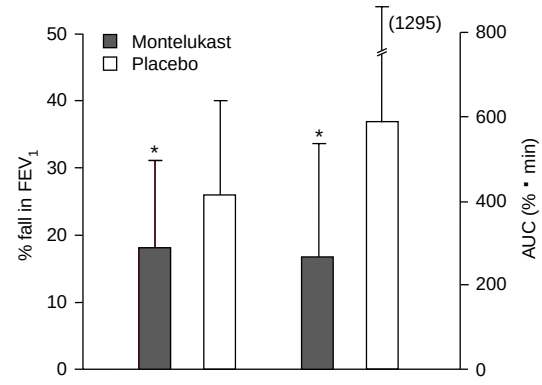

Fig. 1. Montelukast significantly decreased the maximal fall in forced expiratory volume in 1 second (FEV_1) [18 *vs* 26%, $p < 0.05$] and significantly decreased the area under the curve (AUC) for FEV_1 from 0 to 60 minutes following exercise bronchoprovocation compared with placebo (265 *vs* 590% • min, $p < 0.01$).[23]

haled β_2-agonists are the most effective medications for short term protection against EIB, although their protective effect seldom lasts more than 2 hours.[25] Long-acting β_2-agonists have been shown to be effective for at least 9 hours after a single dose when used for EIB.[26] However, with regular administration of salmeterol, even once daily, the bronchoprotective effect may decrease despite the concomitant use of inhaled corticosteroids.[27] In adult patients with asthma, once-daily treatment with montelukast protected against EIB over 12 weeks of treatment without the development of tolerance.[28] Studies comparing the efficacy of montelukast and salmeterol for EIB in adults with asthma have been published.[29-31] These studies demonstrated that the bronchoprotective effect of montelukast was maintained over 8 weeks, while the effect of salmeterol decreased at 4 and 8 weeks.

There are limited data available regarding the efficacy of regular use of cysteinyl-LT receptor antagonists in the treatment of children with persistent asthma. Most studies to date have been in adult populations, although some of these studies included adolescents as young as 12 years. Only one study of the regular use of an LT receptor antagonist in younger children with persistent asthma has been published.[32]

The efficacy and safety of montelukast in children aged 6 to 14 years with asthma were studied during an 8-week double-blind, placebo-controlled trial in 336 patients (201 received montelukast 5mg; 135 received placebo). At baseline, patients had poorly controlled asthma with a mean predicted FEV_1 of 72% and a mean daily requirement of 3.4 puffs of inhaled salbutamol. At study entry, 35% of these patients regularly used inhaled corticosteroids and continued their inhaled corticosteroid during the study. In the montelukast group, there was a significantly greater improvement in FEV_1 from baseline (8.23%) compared with the placebo group (3.58%), and this improvement was maintained throughout the 8-week study. There was a significant decrease in the use of a β_2-agonist for symptom relief, as well as in the percentage of days and the percentage of patients with asthma exacerbations. Asthma exacerbations were defined as follows: a decrease in morning peak flow of more than 20% from baseline; an increase of 70% in the use of a β_2-agonist (or a minimum increase of 2 puffs); an increase of more than 50% in the symptom score from baseline; the patient being awake all night with asthma; or worsening asthma requiring oral corticosteroids, an unscheduled physician visit or emergency room visit, or hospitalisation. In addition, an asthma specific QOL questionnaire[33] revealed a significant overall improvement in QOL and a significant improvement in the QOL instrument domains for symptoms, activity and emotions in montelukast recipients. Of particular interest, positive effects on pulmonary function and QOL were seen in younger and older children, as well as in those receiving concomitant inhaled corticosteroids, for those children receiving montelukast.

Although not a measure of airway eosinophil inflammation, there was also a significant decrease in peripheral blood eosinophil counts over the 8-week treatment period in the montelukast group. This is of interest because it may be an indirect measure of changes in airway inflammation. In one recent study in adults with asthma, montelukast significantly reduced airway eosinophilic inflammation as demonstrated by a 48% decrease in sputum eosinophils in the montelukast-treated group compared with a 23% increase in the placebo group.[34]

With respect to adverse events, in the paediatric study[32] the only significant difference between the montelukast and placebo groups was a greater frequency of allergic rhinitis in the placebo group (possibly a reflection of the positive effect of montelukast on allergic rhinitis). Importantly, there were no significant differences between montelukast and placebo in the prevalence of abnormal liver function tests. The incidence of serum transaminase (AST and ALT) elevations was similar in both groups.

In all paediatric studies of montelukast, approximately 500 patients have been closely monitored.

The overall clinical and laboratory safety profile of montelukast was not significantly different from that with placebo.[35]

There are no long term 'real world' studies of LT receptor antagonists in children with asthma. The closest to such a study is an open label extension study published as an abstract.[36] The effect of montelukast on FEV_1 was consistent during 1.4 years in 201 of the 6- to 14-year-old patients who continued in the open label extension of the study noted above.[32] The increase in FEV_1 was comparable to that in 38 patients who continued in the open label extension of that study, but who were treated with inhaled beclomethasone dipropionate 252µg daily (fig. 2). The change in FEV_1 from baseline was 6.39 *vs* 6.47% for the montelukast and inhaled beclomethasone dipropionate groups, respectively. QOL, as measured by the Asthma Specific Quality of Life Questionnaire (ASQOL) after 4 months, remained significantly improved over baseline and was not significantly different from that in the beclomethasone dipropionate-treated group.[37] This was the case for total ASQOL scores as well as for individual scores for each of the 3 domains (fig. 3).

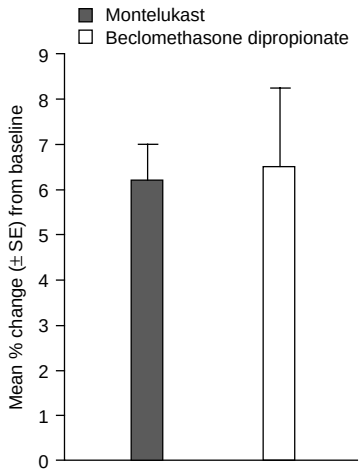

Fig. 2. The increase in FEV_1 in the montelukast group (n = 201) was comparable to that in a control group (n = 38) treated with beclomethasone dipropionate 252µg daily, during an open label extension study.[36]

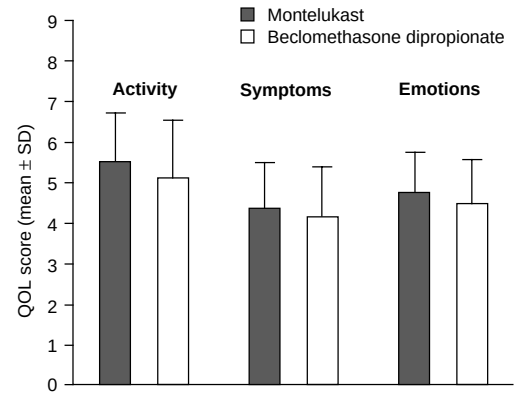

Fig. 3. Effect of montelukast and inhaled beclomethasone dipropionate 252µg daily on the asthma specific quality-of-life (QOL) domains for activity, symptoms and emotions during an open label extension study.[36]

Recent studies published as abstracts show that parents and children prefer once-daily montelukast to inhaled sodium cromoglycate 4 times daily (87% of parents and 82% of children preferred montelukast).[38,39] In those studies, most children taking montelukast were highly compliant (78% of children used >95% of the prescribed medication) compared with sodium cromoglycate (43% of children were highly compliant). Discontinuation of treatment because of worsening asthma was less frequent with montelukast (1%) than with sodium cromoglycate (5%).[38,39]

Conclusion

Montelukast is approved for children aged ≥6 years, whereas zafirlukast is approved for those aged ≥12 years.[1] These LT receptor antagonists may be used in the treatment of children with persistent asthma; however, their place in the therapy of asthma has not yet been completely defined. Studies directly comparing the efficacy and safety of oral montelukast and inhaled corticosteroids for the regular treatment of asthma in childhood are needed. A recently published study in adults with asthma demonstrated that both montelukast

1 Zafirlukast has recently been approved in the US for use in children aged ≥7 years.

and beclomethasone dipropionate had significantly greater effects than placebo; however, beclomethasone dipropionate had a greater mean effect than montelukast.[40] Because concerns relating to the adverse effects of inhaled corticosteroids are frequently raised by parents and physicians, the ability of an LT receptor antagonist to allow for a reduction in the use of inhaled corticosteroids would be important. There are currently 2 published studies in adults demonstrating that pranlukast[41] and montelukast[42] may both successfully allow for a reduction in the inhaled corticosteroid dose. Similar studies in children are essential. Unfortunately, there are as yet no biological markers that allow us to identify patients who are likely to respond to montelukast, or other LT modifiers. Nevertheless, there is good published evidence for the efficacy and safety of montelukast in children aged 6 to 14 years with asthma. Information obtained from the many practitioners who prescribe the new compound will provide feedback from a large number of 'n = 1 studies' regarding its use in the 'real world' and help to define its appropriate role in asthma management.

References

1. Kellaway CH, Trethewie ER. The liberation of a slow-reacting smooth muscle-stimulating substance in anaphylaxis. Q J Exp Physiol 1940; 30: 121-45
2. Brocklehurst W. The release of histamine and formation of a slow reacting substance (SRS-A) during anaphylactic shock. J Physiol 1960; 151: 416-35
3. Kaiser E, Chiba P, Zaky K. Phospholipases in biology and medicine. Clin Biochem 1990; 20: 217-23
4. Griffin M, Weiss JW, Leitch AG, et al. Effects of leukotriene D on the airways in asthma. N Engl J Med 1983; 308: 436-9
5. Marom Z, Shekhamer JH, Bach MK, et al. Slow-reacting substances leukotrienes C4 and D4 increase the release of mucus from human airways in vitro. Am Rev Respir Dis 1982; 126: 449-51
6. Peck MJ, Piper PJ, Williams TJ. The effect of leukotrienes C4 and D4 on the microvasculation of guinea pig skin. Prostaglandins 1981; 21: 315-21
7. Rajah R, Nunn SE, Herrick DJ, et al. Leukotriene D_4 induces MMP-1, which functions as an IGFBP protease in human airway smooth muscle cells. Am J Physiol 271 (Lung Cell Mol Physiol 15): L1014-22
8. Taylor GM, Taylor I, Black P, et al. Urinary leukotriene E_4 after antigen challenge and in acute asthma and allergic rhinitis. Lancet 1989; 1: 584-8
9. Manning PJ, Rokach J, Malo JL, et al. Urinary leukotriene E_4 levels during early and late asthmatic responses. J Allergy Clin Immunol 1990; 86: 211-20
10. Manning PJ, Watson RM, Margolskee DJ, et al. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D4-receptor antagonist. N Engl J Med 1990; 323: 1736-9
11. Kikawa Y, Miyanomae T, Inoue Y, et al. Urinary leukotriene E_4 after exercise challenge in children with asthma. J Allergy Clin Immunol 1992; 89: 1111-9
12. Sampson AP, Castling DP, Green CP, et al. Persistent increase in plasma and urinary leukotrienes after acute asthma. Arch Dis Child 1995; 73: 221-5
13. Smith LJ, Geller J, Elbright L, et al. Inhibition of leukotriene D4-induced bronchoconstriction in normal subjects by the oral./D4 receptor antagonists ICI 204,219. Am Rev Respir Dis 1990; 141: 988-92
14. Wahedna I, Wisniewski AS, Tattersfield AE. Effect of RG 12525, an oral leukotriene D4 antagonist, on the airway response to inhaled leukotriene D4 in subjects with mild asthma. Br J Clin Pharmacol 1991; 32: 512
15. Dahlén B, Kumlin M, Margolskee DJ, et al. The leukotriene-receptor antagonist MK-0679 blocks airway obstruction induced by inhaled lysine-aspirin in aspirin-sensitive asthmatics. Eur Respir J 1993; 6: 1018-26
16. Dahlén B, Zetterström O, Björck T, et al. The leukotriene-antagonist ICI-204,219 inhibits the early airway reaction to cumulative bronchial challenge with allergen in atopic asthmatics. Eur Respir J 1994; 7: 324-31
17. Diamant Z, Timmers MC, van der Veen H, et al. The effect of MK-0591, a novel 5-lipoxygenase activating protein inhibitor, on leukotriene biosynthesis and allergen-induced airway responses in asthmatic subjects in vivo. J Allergy Clin Immunol 1995; 95 (1 Pt 1): 42-51
18. Anderson SD. Is there a unifying hypothesis for exercise-induced asthma? J Allergy Clin Immunol 1984; 73: 660-5
19. McFadden Jr ER. Exercise-induced airway obstruction. Clin Chest Med 1995; 16: 671-82
20. Randolph C. Exercise-induced asthma: update on pathophysiology, clinical diagnosis and treatment. Curr Probl Pediatr 1997; 27: 53-77
21. Manning PJ, Watson RM, Margolskee DJ, et al. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D4-receptor antagonist. N Engl J Med 1990; 232: 1736-9
22. Makker HK, Lau LC, Thomson HW, et al. The protective effect of inhaled leukotriene D_4 receptor antagonist ICI 204,219 against exercise-induced asthma. Am Rev Respir Dis 1993; 147: 1413-8
23. Kemp JP, Dockhorn RJ, Shapiro GG, et al. Montelukast, once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. J Pediatr 1998; 133 (3): 424-8
24. de Benedictis FM, Tuteri G, Pazzelli P, et al. Cromolyn versus nedocromil: duration of action in exercise-induced asthma in children. J Allergy Clin Immunol 1995; 96: 510-4
25. Berkowitz R, Schwartz E, Bukstein MD, et al. Albuterol protects against exercise-induced asthma longer than metaproterenol sulfate. Pediatrics 1986; 77 (2): 173-8
26. Green CP, Price JF. Prevention of exercise induced asthma by inhaled salmeterol xinafoate. Arch Dis Child 1992; 67: 1014-7
27. Simons FER, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. Pediatrics 1997; 99 (5): 655-9

28. Leff JA, Busse WW, Pearlman D, et al. Montelukast, a leukotriene receptor antagonist, for treatment of mild asthma and exercise-induced bronchoconstriction. N Engl J Med 1998; 339: 147-52
29. Turpin JA, Edelman JM, DeLucca PT, et al. Chronic administration of montelukast (MK-476) is superior to inhaled salmeterol in the prevention of exercise-induced bronchoconstriction (EIB) Am J Respir Crit Care Med 1998; 157: A456
30. Villaran C, O'Neill S, Helbling A, et al. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. J Allergy Clin Immunol 1999; 104 (3 Pt 1): 547-53
31. Edelman JM, Turpin JA, DeLucca PT. The Exercise Study Group; Merck & Co., Inc., Horsham, PA, United States. Comparison of oral montelukast, a leukotriene antagonist and inhaled salmeterol in exercise induced asthma (EIA). Eur Respir J 1998; 12: 18s
32. Knorr B, Matz J, Bernstein J, et al. Montelukast for chronic asthma in 6- to 14-year-old children. JAMA 1998; 279 (15); 1181-6
33. Juniper EF, Guyatt GH, Feeny D, et al. Measuring the quality of life in children with asthma. Qual Life Res 1996; 5: 35-46
34. Pizzichini E, Leff JA, Reiss TF, et al. Montelukast reduces airway inflammation in asthma: a randomized controlled trial. Eur Resp J 1999; 14: 12-8
35. Seidenberg BC, Reiss TF. Montelukast – an antileukotriene treatment for asthma. In: Drazen JM, Dahlèn SE, Lee, TH, editors. Five-lipoxygenase products in asthma. New York, NY: Marcel Dekker Inc., 1998: 327-46
36. Noonan G, Reiss TF, Shingo S, et al. Montelukast (MK-0476) maintains long-term asthma control in adults and pediatric patients (aged ≥6 years). Am J Respir Crit Care Med 1999; 159: A640
37. Knorr BA, Matz J, Sveum RJ, et al. Montelukast (MK-0476) improves asthma over 6 months of treatment in 6- to 14-year-old patients. Eur Respir J 1997; 10: 219S
38. Edelman JM, Preston SR, Turpin JA, et al. Parent and child preference for montelukast, a leukotriene receptor antagonist, compared to inhaled cromolyn in asthmatic children ages 6 to 11. Eur Respir J 1998; 12: 18s
39. Edelman JM, Milewski KA, Turpin JA, et al. Effectiveness and safety of montelukast, a leukotriene receptor antagonist, compared to inhaled cromolyn in moderate asthmatic children ages 6 to 11. J Allergy Clin Immunol 1999; 103: S134
40. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. Ann Intern Med 1999; 130 (6); 487-95
41. Tamaoki J, Kondo M, Sakai N, et al. Leukotriene antagonist prevents exacerbation of asthma during reduction of high-dose inhaled corticosteroid. Am J Crit Care Med 1997; 155: 1235-40
42. Lofdahl GG, Reiss TF, Leff JA, et al. Randomised, placebo-controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. BMJ 1999; 319: 87-90

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