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Antileukotrienes as Adjunctive Therapy in Acute Asthma

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Abstract

The leukotriene receptor antagonists (LTRAs) are a comparatively new class of asthma drugs that exhibit both bronchodilator and anti-inflammatory properties. There is a substantial body of evidence for their benefit in the management of chronic asthma in both adults and children, and particularly in specific types of asthma such as exercise-induced and aspirin-sensitive asthma. Despite best practice using current treatment guidelines for the management of acute asthma, a significant proportion of patients require continued treatment and are unable to be discharged from the emergency department; many require a short course of oral corticosteroids. The relatively rapid onset of action of LTRAs after oral administration and their additive effect to β_2-adrenoceptor agonists led to the hypothesis that they might be of benefit in acute asthma. This review examines the available evidence for the effect of LTRAs in acute asthma. Although the evidence is limited, it suggests that treatment with LTRAs provides additional bronchodilator effect to nebulised and inhaled β_2-adrenoceptor agonists. Short-term therapy with LTRAs results in fewer treatment failures and readmissions for patients with acute asthma, and less need for additional therapies such as nebulisers and corticosteroids.

The antileukotrienes or leukotriene receptor antagonists (LTRAs), a relatively new class of drugs for the treatment of asthma, have been available for >9 years. Orally active, they are potent and specific antagonists at the cysteinyl leukotriene-1 (CysLT-1) receptor. They are available as tablets taken once or twice daily and are licensed for the long-term treatment of asthma and allergic rhinitis (in the UK, the license now includes patients with allergic rhinitis who also have asthma). Two oral formulations are available in the UK, several countries in Europe and North and South America, and Japan: montelukast (Singulair™, Merck Sharp & Dohme)[1], available as a once-daily tablet or sprinkle, and zafirlukast (Accolate™, AstraZeneca) a twice-daily tablet. Pranlukast, also an oral agent, is available in Japan only.

1. Leukotrienes in Asthma

Leukotrienes are formed from arachidonic acid by the enzyme 5-lipoxygenase. The cysteinyl leukotrienes (leukotrienes C_4, D_4 and E_4) act via the CysLT-1 receptor.[1] Inflammatory cells such as eosinophils, basophils and mast cells produce cysteinyl leukotrienes.[1-3] Increased amounts of cysteinyl leukotrienes are found in the blood, sputum, and urine of asthmatic patients.[4] The leukotrienes contract airway smooth muscle causing bronchoconstriction – mole for mole they are 1000 times more potent than histamine at contracting airway smooth muscle.[5,6] They also increase airway mucus production, airway wall oedema by increasing vascular permeability, and promote chemotaxis of eosinophils into the airway.[2,7] In aspirin-intolerant

1 The use of trade names is for product identification purposes only and does not imply endorsement.

asthma, inhibition of the enzyme cyclo-oxygenase by aspirin leads to greatly increased levels of cysteinyl leukotrienes, which in turn lead to acute bronchospasm. Importantly, levels of the leukotrienes rise after allergen challenge and exercise, and during an acute asthma attack, and fall as the attack resolves.[1,7]

2. Current Role of the Leukotriene Receptor Antagonists (LTRAs)

The LTRAs work by selectively blocking the action of cysteinyl leukotrienes through the CysLT-1 receptor. All of the LTRAs have been investigated for use in the treatment of chronic asthma. In the UK, montelukast was originally licensed as add-on therapy for patients with asthma incompletely controlled by inhaled corticosteroids and in exercise-induced asthma, and zafirlukast for the long-term treatment of asthma in asthmatics aged ≥12 years.[8-11] Since then, additional studies have been performed that have clarified the place of the LTRAs in the management of asthma. Several studies have compared their effectiveness to long-acting β_2-adrenoceptor agonists and inhaled corticosteroids in patients with asthma of differing severity and ages, and as an alternative therapy to low-dose inhaled corticosteroids (monotherapy). These studies have confirmed that LTRAs are effective therapy for the long-term management of asthma in both adults and children (from the age of 6 months for montelukast).[12] They are effective in chronic asthma in patients already receiving inhaled corticosteroids. In these patients, they reduce asthma exacerbations, improve symptom control, including exercise-induced symptoms, and may allow reduction of inhaled corticosteroid dose. They are also effective in aspirin-sensitive asthma. Studies comparing the efficacy of LTRAs with low-dose inhaled corticosteroids in mild asthma (British Thoracic Society [BTS] step 2 patients) demonstrate that they are less effective as monotherapy than inhaled corticosteroids. Importantly, there is no evidence of tachyphylaxis with long-term use. With this evidence, current asthma guidelines such as the Global Initiative in Asthma (GINA) and BTS guidelines have recommended that they be used in mild to moderate persistent asthma (step 3).[13,14] In the UK, the license for montelukast has recently been extended to include treatment of allergic rhinitis in patients who also have asthma.[15]

3. Acute Asthma

Acute asthma is one of the most frequent reasons for attendance at the emergency department or primary care physician's practice. A substantial proportion of direct asthma costs result from the cost of treating acute asthma. Acute asthma is also responsible for a significant amount of time off work, lost productivity and, in children, time off school.[16] The goal of therapy for an acute asthma attack is 2-fold; first, early resolution of the airway obstruction in the acute attack and, secondly, reduction of the risk of further unscheduled attendances with acute asthma. Despite international guidelines recommending appropriate therapy for acute asthma attacks, they are often poorly managed. In addition, a significant proportion of patients will either not respond to inhaled β_2-adrenoceptor agonists acutely or will subsequently relapse despite apparently adequate therapy.[17] Reducing re-attendance with acute asthma requires review of chronic asthma medications (inhaled corticosteroids, long-acting β_2-adrenoceptor agonists and LTRAs), inhaler technique and adherence to therapy.

Standard therapy is determined by asthma severity upon presentation; mild acute asthma may need only nebulised salbutamol (albuterol) and oxygen.[18] In more severe asthma, frequent nebulised bronchodilators are required and systemic therapy with a corticosteroid may be necessary. Although corticosteroids are effective, they usually take 4–6 hours to confer benefit and studies demonstrating a reduction in hospitalisation have reported conflicting results.[19,20] Other drugs, such as nebulised anticholinergics and magnesium, have been used in the treatment of acute asthma. A recent meta-analysis suggesting that nebulised ipratropium bromide can reduce hospitalisation rates has supported its use as adjunctive therapy in more severe acute asthma.[21] The most recent BTS/Scottish Intercollegiate Guidelines Network (SIGN) guidelines have also suggested that intravenous magnesium may be useful in acute severe asthma.[14]

Ideal treatment of an acute attack would involve a rapid improvement in airway obstruction that could be maintained, thus reducing the need for further β_2-

Table I. The effect of administration of a leukotriene receptor antagonists (LRTAs) on clinical parameters in acute asthma

LTRA (dose and route)	Baseline FEV_1 [L] (% predicted)	Maximum increase in FEV_1 (%)	Time to peak effect (h)	Discharge from the ED?	Reduction in need for other medications	Reference
Montelukast (7mg IV)	2.5 (63.8)	33.57	2	Not measured	Not measured	23
Montelukast[a] (14mg IV)	1.6 (44.8)	19.5	1	Fewer treatment failures[b]	Reduced need for corticosteroids; reduced β-agonist nebulisations	24
Montelukast (10mg PO)	56.7[c]	42[c,d]	2	Not measured	Reduced β-agonists	25
Zafirlukast (160mg PO)	1.24 (37.8)	26	4	Yes, relative risk reduction of 34%	Not measured	26

a Mean difference between montelukast and placebo 14.1% at 2h (absolute change from baseline of ≈28%).

b Need for hospitalisation or additional therapies.

c Peak expiratory flow rate measured not FEV_1.

d Corticosteroid (prednisolone 1mg/kg) plus montelukast (39.9% for montelukast alone).

ED = emergency department; **FEV_1** = forced expiratory volume in 1 second; **IV** = intravenous; **PO** = oral.

adrenoreceptor agonist therapy, corticosteroids and hospitalisation. However, as significant numbers of patients with asthma presenting with an acute attack require hospitalisation, many of whom do not respond acutely to short-acting β_2-adrenoceoptor agonists, there is a need for new therapies.

4. Mechanism of Action of LTRAs in Acute Bronchospasm

The observation that urinary leukotriene E_4 levels rise during an acute asthma attack and fall as it resolves has led to speculation that they have a significant role to play in the bronchospasm typical of an acute asthma attack. This was further supported by an early study of zafirlukast.[22] Administration of a single oral dose of zafirlukast 20mg was followed by a short-term improvement in forced expiratory volume in 1 second (FEV_1) within a few hours, which suggested that leukotrienes could be contributing to basal airway tone. The leukotrienes mechanism of action was not through the β_2-adrenergic receptor, as inhaled or nebulised salbutamol caused more bronchodilatation and improvement in FEV_1. Since then, it has been shown that specific leukotriene receptors exist in the lung for both the cysteinyl leukotrienes and for leukotriene B_4 (LTB_4).

5. The Potential Benefit of LTRAs in Acute Asthma

There is a substantial body of evidence for the effect of LTRAs in chronic asthma, where the effect is thought to be due to blockade of cysteinyl leukotrienes and also an anti-inflammatory effect, targeting the eosinophils in particular. However, there are few studies of the effect of LTRAs in acute asthma. As discussed in section 1, there are theoretical reasons why the LTRAs might be of benefit in acute asthma. It seems logical that with the increased production of leukotrienes during an acute attack, the LTRAs might be particularly efficacious. A small number of studies have now been performed to determine whether two LTRAs, montelukast and zafirlukast, are effective in the treatment of acute asthma (table I).

5.1 Single-Dose Studies: Oral versus Intravenous

In the last few years, the possibility that LTRAs might be of benefit in acute asthma has been explored. However, the LTRAs are given orally, which delays their onset of action and therefore their potential benefit. Thus, an initial study was performed with an intravenous formulation of montelukast to determine the rapidity of effect and maximal effect achieved over 24 hours after administration.[23] Two doses of montelukast were chosen (7mg intravenously and 10mg orally) and compared

with placebo in 51 asthma patients aged >15 years, using a double-blind, single-dose, three-period crossover design. An earlier study[27] had shown that the plasma concentration-time profile of intravenous montelukast was proportional to the dose over the range 3–18mg and data suggested that 7mg intravenously was equivalent to 10mg of montelukast orally. Subjects had moderate stable asthma (mean FEV_1 63%); 25% were also taking a stable dose of inhaled corticosteroids. Interestingly, the study showed that over the 24-hour period, the single intravenous dose of montelukast (7mg) resulted in more bronchodilatation than the 10mg oral dose (mean increase in area under the curve from time zero to 24 hours [AUC_{24}] 20.7% for 7mg intravenously vs 15.72% for 10mg orally). In addition, as expected with an intravenous formulation, the onset of action was faster than for the oral preparation, with the mean percentage change in FEV_1 being 15.02% versus 4.67% at 15 minutes, and rising to 18.43% versus 12.90% at 1 hour. The change in placebo was 3.05% at 15 minutes and maximal at 7.33% at 1 hour. The rise in FEV_1 was maintained for 24 hours with both the intravenous and the oral preparation, and while the results favoured the intravenous preparation, it did not reach statistical significance. It was also interesting in that the lower intravenous dose appeared to be more effective than the oral dose despite previous plasma concentration-time profile data, which suggests that perhaps more benefit could be obtained from higher oral doses of montelukast.

The single-dose study, demonstrating a very significant improvement within 15 minutes of administration, suggested that further studies in acute asthma were warranted. A subsequent pilot study determined the efficacy of intravenous montelukast in acute asthma. This randomised, double-blind, parallel group, multicentre study looked at the effect of intravenous montelukast or matching placebo in addition to standard therapy (short-acting β_2-adrenoceptor agonists and corticosteroids) in 201 patients presenting with moderate to severe acute asthma.[24] Two doses of montelukast (7mg and 14mg) were used in order to demonstrate any additional improvement with a higher dose. The clinical outcome was short-term improvement in airflow obstruction over 1 hour (as measured by change in FEV_1). Additional clinical outcomes were hospitalisation or need for prolonged or additional anti-asthma therapy. All patients discharged from the emergency department were given a 5-day course of oral prednisone and a 2-week follow-up appointment. These patients had quite severe asthma on presentation; mean FEV_1 was 39.2% after at least one salbutamol nebuliser, and those with an initial good response to salbutamol (FEV_1 >70% predicted) were excluded. The FEV_1 immediately before allocation to study drug was 44.8% for montelukast (both groups) and 50.1% for placebo. Both doses of montelukast caused a significant improvement in FEV_1 within 10 minutes of administration. There was no significant difference between the two intravenous doses and both were significantly different from placebo ($p \leq 0.05$). Those patients receiving montelukast had less need for salbutamol nebulisers over the treatment period (1 hour) and received corticosteroids less often (59.3% vs 75.8% placebo). Unfortunately, adding montelukast to standard therapy did not reduce the number of patients who required hospitalisation for their asthma. Neither did it reduce the number of unscheduled asthma-related repeat visits to the emergency department, hospitalisations, doctor visits or need for rescue corticosteroids in the first 14 days after the study period. This is perhaps not surprising given that the patients received only one dose of montelukast and that discharge medication was a short course of oral corticosteroids; no mention was made of regular anti-asthma therapy, which would have had more impact on asthma control in the month following the acute asthma attack. This was a pilot study to demonstrate efficacy; thus, patients did not receive other short-term asthma medications. As there is some evidence for the benefit of short-term anticholinergics, particularly in severe asthma, it would be of interest to see if patients derived additional benefit from an LTRA in the presence of both salbutamol and ipratropium bromide nebulisers in a future study.

5.2 The Role of Oral LTRAs in the Treatment of Acute Asthma

Two studies have examined the efficacy of an oral LTRA in the treatment of acute asthma. In the first, the effect of adding montelukast 10mg to intra-

venous corticosteroid (prednisolone 1mg/kg), corticosteroid alone or placebo was evaluated over 24 hours in 70 patients.[25] These treatments were given before any other treatments; they were followed by aerosolised terbutaline (0.5mg at 20-minute intervals for 1 hour). Following this, patients were evaluated for 24 hours to determine the effect on peak expiratory flow rate (PEFR), Borg breathlessness score and the need for rescue medication. As patients were enrolled from both the emergency department and outpatient clinics, the acute asthma attacks were less severe; the average PEFR was ≈56% of predicted. Both those receiving intravenous corticosteroid alone and those receiving intravenous corticosteroid plus montelukast significantly improved over the 24 hours; the comparison between corticosteroid alone and montelukast plus corticosteroid favoured montelukast plus corticosteroid but did not reach statistical significance. The percentage change from baseline in PEFR was +42% for montelukast plus corticosteroid, +39.9% for corticosteroid alone and +10.3% for placebo. Dsypnoea scores decreased in both active treatment groups compared with placebo, and the montelukast plus corticosteroid group required fewer aerosolised short-acting β_2-adrenoceptor agonists (0.8 vs 1.6 inhaler puffs). Unfortunately, the study did not report hospitalisations or need for a course of oral corticosteroids, and there is no follow-up information on patient outcome after the initial 24 hours.

In the second study, a total of 641 patients attending the emergency department with acute asthma were randomised to receive either a single dose of zafirlukast (160mg or 20mg) or placebo as an adjunct to standard care for acute asthma if their FEV_1 was <70% predicted 25 minutes after an initial dose of nebulised salbutamol.[26] All patients also received oral prednisone 60mg and additional salbutamol nebulisers at hourly intervals. At 4 hours, patients were assessed and a decision regarding 'extended care' (additional time in the emergency department or admission) or discharge was made. Although no formal criteria for discharge were included in the study, investigators were encouraged to follow the National Asthma Education and Prevention Program to decide on criteria for discharge. Patients discharged at 4 hours who had been given zafirlukast continued to receive zafirlukast 20mg twice daily for 40 days; patients receiving placebo received matching placebo twice daily. All patients received a 7-day course of oral corticosteroids, were given a salbutamol inhaler and asked to resume their usual asthma medications. Patients were contacted by telephone and then seen at 10 days and 28 days after discharge and contacted once more 14 days later. The primary outcome measure was time to relapse after discharge, rather than short-term improvement in lung function in the emergency department. Secondary outcome measures included the percentage of patients needing extended care in the hospital, improvement in FEV_1 and shortness of breath, and, after discharge, PEFR and asthma symptoms. Although this was the only study to report the required sample size for its outcome measure, it failed to enrol sufficient patients. Despite this, the study showed that 23.6% of the high-dose zafirlukast recipients relapsed during the 28-day outpatient period, compared with 28.9% of those receiving placebo ($p = 0.047$). Most of the relapses were patient-initiated unscheduled doctor or emergency department visits with worsening asthma. By the end of 4 hours in the emergency department, only 9.9% of those receiving zafirlukast 160mg, 16.5% of those receiving zafirlukast 20mg and 15% of those receiving placebo required extended care (a relative risk reduction of 34% for zafirlukast 160mg vs placebo; $p = 0.052$). Not surprisingly, all patients experienced an improvement in FEV_1 and reduction in breathlessness scores. Following discharge, lung function improved significantly more in patients receiving zafirlukast than in those receiving placebo ($p = 0.008$). This is the only study to show that the addition of an LTRA can reduce both extended care and relapse rate in patients with acute asthma.

6. Conclusion

There are few studies evaluating the effect of an LTRA in acute asthma and they are limited by the lack of clinically relevant outcomes such as hospitalisation and relapse rates. In addition, withholding usual asthma therapies makes it difficult to determine the value of the LTRAs over and above standard therapy for acute asthma. The single-dose oral and intravenous montelukast study did show a significant acute bronchodilator response, but in the follow-up pilot study, this effect did not result in

reduced hospitalisation or relapse rates. The single study with oral montelukast demonstrated reduced requirement for nebulised terbutaline, but hospitalisation rates were not reported. In contrast, the study with zafirlukast, in which patients were treated both acutely and on discharge from the emergency department, demonstrated a reduction in the number of patients requiring a longer stay in the emergency department and/or hospitalisation, a lower relapse rate and greater improvement in lung function.

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References

1. O'Byrne P. Leukotrienes in the pathogenesis of asthma. Chest 1997; 111 (2 Suppl.): S27-34
2. Laitinen LA, Laitinen A, Haahtela T, et al. Leukotriene E4 and granulocytic infiltration into asthmatic airways. Science 1982; 216: 196-8
3. Wenzel SA. The role of leukotrienes in asthma. Prostaglandins Leukot Essent Fatty Acids 2003; 69: 145-55
4. Sampson AP, Pizzichini E, Bisgaard H. Effect of cysteinyl leukotrienes and leukotriene receptor antagonists on markers of inflammation. J Allergy Clin Immunol 2003; 111 (1 Suppl.): S49-59
5. Holgate ST, Peters-Golden M, Panettieri RA, et al. Role of cysteinyl leukotrienes in airway inflammation, smooth muscle function and remodelling. J Allergy Clin Immunol 2003; 111 (1 Suppl.): S37-42
6. Barnes NC, Kuitert L. Influence of leukotriene receptor antagonists on baseline pulmonary function and asthmatic responses. Adv Prostaglandin Thromboxane Leukot Res 1994; 22: 217-26
7. Sampson AP, Green CP, Spencer DA, et al. Leukotrienes in the blood and urine of children with acute asthma. Ann N Y Acad Sci 1991; 629: 437-9
8. Reiss TF, Chervinsky P, Dockhorn RJ, et al. Montelukast, a leukotriene receptor antagonist, in the treatment of chronic asthma. Arch Int Med 1998; 158: 1213-20
9. Leff JA, Busse WW, Pearlman D, et al. Montelukast, a leukotriene receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. N Engl J Med 1998; 339: 147-52
10. 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: 424-8
11. Barnes NC, Miller CJ. Effect of leukotriene receptor antagonist therapy on the risk of asthma exacerbations in patients with mild to moderate asthma: an integrated analysis of zafirlukast trials. Thorax 2000; 55: 478-83
12. van Adelsburg J, Moy J, Wei LX, et al. Safety, tolerability, and exploratory efficacy of in 6- to 24-month-old patients with asthma. Curr Med Res Op 2005; 21: 971-9
13. National Institutes of Health 2002. Global initiative for asthma: global strategy for asthma management and prevention 02-5075. Bethesda (MD): National Heart, Lung and Blood Institute: 1-178 [online]. Available from URL: http://www.ginasthma.com [Accessed 2007 Feb 21]
14. British Thoracic Society/SIGN British Guideline on the Management of Asthma November 2005 update [online]. Available from URL: http://www.enterpriseportal2.co.uk/filestore/bts/asthmaupdatenov05.pdf [Accessed 2007 Feb 21]
15. Nayak A, Langdon RB. Montelukast in the treatment of allergic rhinitis: an evidence-based review. Drugs 2007; 67 (6): 887-901
16. Weiss KB, Sullivan SD, Lyttle CS. Trends in the cost of illness for asthma in the United States 1985-1994. J Allergy Clin Immunol 2000; 106: 493-9
17. Emerman CL, Woodruff PG, Cydulka RK, et al. Prospective multicentre study of relapse following treatment for acute asthma among adults presenting to the emergency department. Chest 1999; 115: 919-27
18. Strauss L, Hejal R, Galan G, et al. Observations on the effects of aerosolised albuterol in acute asthma. Am J Respir Crit Care Med 1997; 155: 454-8
19. Rowe BH, Spooner C, Ducharme FM, et al. Early emergency department treatment of acute asthma with systemic corticosteroids (Cochrane Review). In: Lasserson T, Picot J, editors. Available in The Cochrane Library [database on disk and CD ROM]. Oxford: Oxford Update Software, 2001
20. Rodrigo G, Rodrigo C. Corticosteroids in the emergency department therapy of acute asthma: an evidence-based evaluation. Chest 1999; 116: 285-95
21. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med 1999; 107: 363-70
22. Hui KP, Barnes NC. Lung function improvement in asthma with cysteinyl-leukotriene receptor antagonist. Lancet 1991; 337: 1062-3
23. Dockhorn RJ, Baumgartner RA, Leff JA, et al. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. Thorax 2000; 55: 260-5
24. Carmargo CA, Smithline HA, Malice M-P, et al. A randomised controlled trial of intravenous montelukast in acute asthma. Am J Respir Crit Care Med 2003; 167: 528-33
25. Cylly A, Kara A, Ozdemir T, et al. Effects of oral montelukast on airway function in acute asthma. Respir Med 2003; 97: 533-6
26. Silverman RA, Nowak RM, Korenblat PE, et al. Zafirlukast treatment for acute asthma: evaluation in a randomised, double-blind, multicenter trial. Chest 2004; 126: 1480-9
27. Cheng H, Leff JA, Amin R, et al. Pharmacokinetics, bioavailability, and safety of montelukast sodium (MK-0476) in healthy males and females. Pharm Res 1996; 13: 445-8

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