INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY Vol. 15, no. 3, 171-182 (2002)

REVIEW ARTICLE

THE ROLE OF ANTILEUKOTRIENES IN THE TREATMENT OF ASTHMA

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Received May 31, 2002 - Accepted July 16, 2002

Cysteinyl leukotrienes (Cys-LTs) are mediators released in asthma and are both direct bronchoconstrictors and proinflammatory substances that mediated several steps in the pathophysiology of chronic asthma, including inflammatory cells recruitment, vascular leakage, and possibly airway remodelling.

Available evidence from clinical trials and real-word experience derived from managing patients with asthma justifies a broader role for anti-LTRAs in asthma management than that recommended in the National Asthma Education and Prevention Programm (NAEPP) and National Health Lung and Blood Institute (NHLBI) treatment guidelines.

Leukotriene-receptor antagonists drugs (LTRAs) seem to be effective alternatives to inhaled corticosteroids (ICS) either as monotherapy or as adjunctive therapy that reduces the need for higher doses of ICS in patients with mild-to-moderate persistent asthma. LTRAs may be used as adjunctive therapy for al levels of disease severity because they are effective in combination with ICS during long-term maintenance therapy. The agents seem especially effective in preventing aspirin-induced asthma, exercise-induced asthma (EIA) and they may provide an additional advantage of reducing nasal congestion in patients with both asthma and rhinitis.

Asthma is a serious disease characterized by reversible airflow obstruction, airway hyper-responsiveness (AHR), and allergic inflammation (1). The inflammatory process in the airways plays a significant role in the pathogenesis of asthma, making it an important target for anti-asthma pharmacotherapy. The process is often a consequence of allergic response to pollen, dust, and other antigens. Allergic response involves infiltration of activated eosinophils (EOS) and T-lymphocytes, and degranulation of mast cells, which lead to the release of numerous chemical mediators that cause physiologic changes in the airways such as smooth muscle contraction, oedema, and increased in mucus secretion.

One of the most implicated mediators in asthma pathogenesis are the leukotrienes (LTs), which are lipoxygenase products from arachidonic acid (AA) metabolism. They are released from lung tissue of asthmatic patients and purified from human lung mast cells by antigens. The use of anti-leukotriene agents, such as LTs biosyntesis inhibitors and leukotriene antagonists (LTRAs) has been found to reverse the bronchoconstrictive effects of LTs and significantly improve asthma symptoms. LTRAs have proven efficacious in

Key words: Leukotriene, leukotriene receptor antagonists, asthma, inhaled corticoteroids, airway hyperresponsiveness, rhinitis

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0394-6320 (2002)

randomised, controlled clinical trials (RCTs) of asthmatic adults, children and even preschool children. They have been rapidly introduced into clinical practice worldwide, although their position in treatment guidelines is still evolving. LTRAs have several features that are likely to promote good results to treatment and are generally well tolerated. The available clinical data suggest that LTRAs should be considered as a therapeutic option or as additive therapy in patients with mild to severe asthma.

NATURAL HISTORY OF ASTHMA

Genetics

It is generally accepted that both genetic and environmental factors determine the phenotypic expression of this complex disease. Several recent studies have investigated "asthma-like" phenotypes such as AHR, a hallmark of asthma, in the inbred mouse, given the high degree of homology between the mouse and human genomes. These studies have definitely shown that AHR is under genetic control in the inbred mouse. Two of these early studies measured AHR in a large number of inbred strains and demonstrated that different inbred strains of mice display varying degrees of AHR in response to bronchoconstrictors (2,3). The results of these studies established the inbred mouse as an ideal species for dissecting out the genetic factors contributing to this phenotype. Later studies were performed in order to identify genes or chromosomal regions that contribute to AHR phenotype. Within these regions lie several candidate genes implicated in the pathobiology of asthma (4). Subsequent studies are being performed with knockout mice and transgenic mice to investigate the role of these candidate genes on AHR (5-7).

Childhood

The greatest incidence of childhood asthma is among males under five years of age, with decreasing numbers of new cases in the later years. The predominant feature associated with asthma in children is allergy, and it appears that dust mites represent the major allergens causing asthma throughout the world (8). Several studies clearly demonstrate a strong relationship between allergen exposure, especially mite-allergen exposure, and risk of sensitisation (9,10).

Boys suffer from asthma more often than girls (11). This may be related to the airway size, which is smaller in males and so the greater prevalence of allergy in boys.

It is estimated that 30-50% of children have asthma that disappears at puberty, but asthma often "reappears" in adult life (12-14). Between a third and two thirds of asthmatics children continue to suffer from the disease in adult life. The prognosis of the disease is poorer if it first develops at a very young age, or if it is serious (particularly if it resulted in hospitalisation for asthmatic attack or serious illness).

Adults

Studies on adults shown similar prevalence of persistent and episodic asthma, but in addition, some adults appear to have asthma in remission (15). In the general adult population, eosinophilia is associated with AHR both in symptomatic and asymptomatic subjects, where as skin test is positively associated with AHR only in symptomatic subjects (16).

Asthma onset can occur in adult life in response to sensitising agents in the workplace and, in some non affluent societies, from the development of atopy later in life (15). However, late-onset asthma is often non-allergic. Viral infections may still, in adult life, be a trigger for asthma attacks even in patients with episodic asthma. Studies of the natural history of asthma support the hypothesis that early therapeutic intervention in mild disease may lead to an improved clinical outcome (17).

INFLAMMATORY EFFECTS OF LEUKOTRIENES

Recently asthma has been defined as a "chronic inflammatory disorder of the airways" in which many cells and cellular elements play a role, particularly mast cells, EOS, T-lymphocytes, NEU, and epithelial cells, and an emphasis has been placed on the use of anti-inflammatory agents for treatment (1).

The LTs comprise a group of inflammatory mediators that are derived from metabolism of AA by 5-lypoxygenase (5-LO). The LTs with cysteine residues, LTC4, LTD4 and LTE4, are bronchoconstrictors that are up 1,000 times more potent than histamine in causing bronchoconstriction. The Cys-LTs are also asso-

ciated with increased vascular permeability, mucus production, cellular infiltration of the airways and decreased mucociliary transport. LTB4, which does not have a cysteine residue, determine aggregation and chemotaxis of polymorphonulclear leucocytes (PMNs), exudation of plasma, translocation of calcium and chemokinesis of PMNs (18-20).

The observation that Cys-LTs are proinflammatory would naturally suggest that LTRAs should have beneficial effects on inflammation (21).

Clinical studies of LTRAs in mild to moderately severe asthma have generally shown a rapid improvement in lung function within the first 1 to 2 days of starting treatment with no further improving following this (22). Studies with montelukast have also shown a gradual fall in peripheral blood eosinophil count which would indicate an effect on an important inflammatory cell in the airways (23).

One possible clinical expression of this effect on airway eosinophilia may be the decrease in asthma exacerbations demonstrated in trials of montelukast (23) and a meta-analysis of studies with zafirlukast in mild to moderately severe asthma (24). Confirmation that montelukast has anti-inflammatory effects comes from an induced sputum study in mild to moderately severe asthma (25). It is clear that LTRAs have a dual action, relieving the effects of an endogenous bronchoconstrictor and having an effect on airway inflammation. However, the relative importance of these two actions for the clinical effects of these drugs is not fully understood at present.

EFFICACY OF INHALED CORTICOSTEROIDS

ICS are widely accepted as highly efficacious drugs for the treatment of persistent asthma. In clinical trials, ICS have consistently shown improvement in pulmonary function parameters, such as peak expiratory flow (PEF) and forced expiratory volume in one second (FEV1). ICS are also known to improve symptoms, decrease rescue short acting β2-agonists (SABA) use and decrease exacerbations. In addition to improving airway obstruction, they are the only drugs known to modestly impact AHR, generally improving methacholine reactivity in the range of two-four fold (26,27). Their effects in decreasing inflammation evaluating with lymphocityc or eosinophilic markers, have been significant and consistent from study to study; however, the studies have generally utilised high doses of ICS for two or three months (28). In addition to the problem of compliance, the potential of ICS to cause adverse systemic effects in children, particularly at high dosages, is another factor giving rise to concern about their use. The main areas of concern center around the possible effects on the hypothalamic-pituitary-adrenal axis growth and bone metabolism and density (possible risk of osteoporosis) (29). Low doses of ICS (<400 μg/day) are not normally associated with evident systemic effects in children; however, the risk of such adverse effects increases when doses > 800 μg/day as needed to control asthma symptoms. In particular, significant inhibitory effects on short-term and intermediate-term growth have been reported with high dosage of ICS. In children with very mild asthma, there may even be an effect on growth with doses of ICS as low as 400 μg/day of beclomethasone dipropionate or equivalent (30). It has been shown that, at 400 μg/day, there is a consistent effect on nocturnal cortisol profiles and morning urinary free cortisol, which demonstrates there is a systemic effect even of moderately low doses (31).

EFFECTS OF LTRAs

The LTRAs, including montelukast, zafirlukast and pranlukast, selectively block the binding of the Cys-LT1 receptor, which has been identified as the receptor through which most of their actions as bronchoconstriction, mucus hypersecretion and increased vascular permeability and EOS migration (32).

Moreover, LTRAs prevent many types of provoked asthmatic responses, including allergen-induced, exercise- and cold air hyperventilation-induced, and aspirin-induced asthma (AIA) (32,33).

Studies have examined the effects of the LTRAs on bronchoconstriction and inflammation. The LTRAs protect against bronchoconstriction induced by exogenous LTs, sulfur dioxide, cold air, platelet-activating factor, and allergens (34-36).

On administration to patients with asthma, the LTRAs also cause significant decreases in various inflammatory cells, including EOS, T-lymphocytes, and mast cells, as well as modifica-

tions in mediator release and activation response to segmental antigen challenge (37-39). Studies also have demonstrated that the LTRAs are associate with a decrease in hyperresponsiveness, a potential marker of inflammation (40-42).

Various studies have shown that LTRAs inhibit exercise-induced-asthma (EIA) (43-45), and have also been shown to improve FEV1, asthma symptoms and SABA use in clinical trials, including trials in children (46-48). Multiple clinical trials have supported an effect on exacerbations and a decrease in the need for steroid rescue in studies of 3-12 months duration (49). Quality of life (QoL) also consistently improved (40).

THE PLACE OF LTRAs IN THE MANAGEMENT OF ASTHMA

The prevalence of childhood asthma has increased over the past few decades, as have hospitalizations for the disease (50,51). These increases have been mirrored by a dramatic rise in the use of anti-asthma drugs. Morbidity indices show little evidence of improvement despite the high rates of prescription of asthma drugs. This may be because of a failure to use asthma prophylaxis consistently (52). Moreover, there is no evidence that any therapeutic intervention modifies the natural history of the disease.

Management of childhood asthma has over the previous 30 years become entrenched in the use of long acting β2-agonist (LABA) and ICS, with the prejudice that oral therapy will not offer any significant benefit, other than with the use of ICS for acute exacerbation.

Poor compliance with regular inhaled therapy compromised the ability to achieve effective control. ICS are usually introduced when intermittent SABA fail to control symptoms or when there is abnormal spirometry between episodes or, in milder cases, after a trial using cromolyn sodium has been unsuccessful (53). However, some children fail to respond to ICS therapy, the most common reason being lack of compliance with inhalants (53,54).

Moreover, many patients require relatively high doses of ICS, which has engendered inevitable concern about long-term adverse systemic effects and EIA symptoms have often not been adequately prevented without the use of frequent doses of SABA. On the other hand, the development of tolerance resulting from continuous use of β2-agonists is of concern.

Overall, these limitations with existing treatments have highlighted the need for additional modalities of therapy. Against the above described background, the development of an orally active, once-daily, disease-modifying drug with additional bronchodilator properties would represent a major advance for managing young patients with asthma.

As it will be outlined in this review, LTRAs answer to such prerequisites of an ideal drug for treating asthma in children: firstly, they are orally active to encourage optimal medication compliance: compliance with oral pills is approximately 80% (vs<50% for inhalers) in patients with asthma (55). Indeed, a recent patient-parent preference/satisfaction study demonstrated superiority of montelukast over cromolyn in asthmatic patients with regard to both compliance and patient-parent preference (56). Secondly, they have a long duration of action, requiring less frequent administration; they have anti-inflammatory and disease modifying properties, as well as bronchodilator effects to improve symptoms; they have a favorable tolerability profile, both in infants and older children; lastly, they have beneficial effects on other atopic manifestations commonly associated with asthma, such as allergic rhinitis and atopic dermatitis.

RESULTS OF CLINICAL TRIALS WITH MONTELUKAST AND ZAFIRLUKAST IN CHILDHOOD ASTHMA

In the United States, montelukast and zafirlukast are approved for use in children, montelukast for children 2 years and older (57-58) and zafirlukast for children 7 years and older (59-61).

Montelukast

Montelukast (Merck & Co, Inc, Whitehouse Station, NJ) is an orally bioavaliable Cys-LTRA administered once daily. The drug has been approved for the treatment of asthma in children 2 years and older. Therapeutic concentrations of montelukast does not inhibit the cytochrome P450 isoenzymes (62-63).

Montelukast provides significant improvements in measures of lung function and QoL in both adult and paediatric patients with chronic asthma, irrespective of the use of ICS, with a tolerability profile similar to placebo. In a

multicenter, double-blind, placebo controlled trial montelukast (5 mg once daily) was compared with placebo in 336 children aged 6-14 years, with moderate to severe asthma (mean FEV1 72% predicted; 2-3 daily doses of ß2-agonist; 1-2 nocturnal awakenings per week attributable to asthma), one third of whom on ICS at a constant dose (37). After the 8-week treatment period, both the percentages of days, and of patients, with asthma exacerbations were significantly lower in the group receiving montelukast ($p=0.049$ and $p=0.002$, respectively, vs placebo). Asthma-specific quality of life (AQLQ) parameters improved with montelukast (40). The change from baseline in the montelukast group was significantly greater ($p<0.007$) than that in the placebo group for the three quality of life domains assessed (activity, symptoms, and emotions) particularly for the activity domain. A similar result was shown with regard to the morning forced expiratory volume in one second (FEV1), which increased by a mean of 8% (compared to 4% in the placebo group). The onset of action of montelukast, as reflected in the requiring of beta agonist bronchodilators over the first 3 weeks of treatment, was rapid and was observed within one day of starting therapy. In a subsequent extension of the study, in which children received either montelukast or an ICS for periods of up to 1.4 years, the improvement in percentage of predicted FEV1 values with montelukast was maintained, with a similar change from baseline to that in the ICS group (6.5% and 6.4%, respectively). Tolerance does not develop with montelukast (64).

In a group of asthmatic preschool children < 6 years old cold-air hyperventilation caused a 17% increase in airway resistance after pretreatment with montelukast, compared with 47% increase after placebo, showing the bronchoprotective effect of this LTRA (65-66).

In a RCT of 689 children 2- to 5 years old with physician-diagnosed asthma, 12 weeks of montelukast caused a significant reduction in days with symptoms, daytime asthma symptoms scores, days of ß-agonist use, and peripheral blood eosinophils, with a significant improvement in asthma control (66).

Five RCTs were reported on the effects of 3 to 12 weeks of treatment of montelukast over placebo on chronic asthma in adults. The patients included were adult asthmatics with moderate to severe asthma (mean Fev1 60-68% predicted; 5-6 daily puffs of inhaled ß-2 agonists and 4-6 nocturnal awakenings for week attributable to asthma), yet without concurrent treatment with steroid. Montelukast showed an effect over placebo on daily asthma symptoms, use as-needed medication, asthma exacerbations, nocturnal awakenings, and baseline lung function (42, 67-70).

ICS were more efficacious than montelukast in a RCT of adult patients with moderate to severe asthma (71).The complementary effect of montelukast to that of established treatment with beclometasone dipropionate (BDP) was reported in 2 RCT (70-72). In patients benefiting from but incompletely controlled on inhaled BDP, the addition of montelukast provided significantly improved lung function, symptom control, and reduced exacerbation rates compared with BDP monotherapy, and allowed tapering of the steroid dose (70). Montelukast provided some bronchoprotection against EIB in mild asthmatic adults (43).

Zafirlukast

Zafirlukast (AstraZeneca, Wilmington, DE) is a Cys-LTRA approved for treatment of asthma in children 7 years old and older (73). It is administered orally twice daily and is metabolized by the liver, and hepatic cytochrome P450 is inhibited by therapeutic concentration of zafirlukast. Therefore, there is a risk of drug interaction, and transient elevations of liver enzymes have been reported (74).

Three RCTs hav reported the effect of 3 to 12 weeks treatment with zafirlukast over placebo. The patients included were adult asthmatics with moderate to severe asthma (mean FEV1 60-68% predicted; 5-6 daily doses of inhaled SABA and nocturnal awakenings for week attributable to asthma), yet without concurrent treatment with steroid (47, 75-76). In these studies were demonstrated a dose-related clinical effect on daily asthma symptoms, use of as-needed medication, and baseline lung function.

In a randomized double-blind, 3-way, crossover study of 39 asthmatic children from 6 to 14 years old, zafirlukast, 5,10, 20 and 40 mg and placebo were tested for their effects on EIB. At exercise challenge at 4 hours after dosing, treatment with

zafirlukast attenuated the maximal percentage decrease in FEV1 compared with placebo with no apparent dose-response relation in the range of 5 to 40 mg (77). FEV1 improved by 11% over placebo and use of ß2-agonist decreased by up to 1 puff per day and nocturnal awakenings by 2.6 per week as compared with placebo (75). The number of symptomatic days were reduced from 27 to 24 per month, and the number of days without use of ß-2 agonist increased from 6.0 to 11.3 per month. The number of health care visits decreased from 0.40 to 0.19 for month (53). These effects seem modest, although statistically significant.

CLINICAL TRIALS OF LTRAs IN TODDLERS AND INFANTS

Most children with chronic asthma first show symptoms as toddlers or infants. ICS are effective in treating moderate to severe asthmatic symptoms in infants or toddlers (78-79). However, safety is of particular concern in such patients, and inhalation therapy is cumbersome for some of these children. Therefore, ICS are only used in children with persistent symptoms.

Patients with mild symptoms for whom steroid treatment is not appropriate are often treated with regular oral bronchodilators (with little documented efficacy) or with LABA. Intermittent treatment of young children with short term relievers is often insufficient and a long-term treatment effect would be of importance for young children. Two pediatric trials addressed the effect of montelukast on 2- to 5-year-old asthmatic children, showing bronchoprotection and reduction in symptoms, need for rescue treatment, asthma exacerbations, and peripheral eosinophils (65-66).

In conclusion, LTRAs, because of their oral administration, good safety profile, prolonged effect, and partial antiinflammatory effects, may play an important role as first-line treatment of young wheezy children with mild recurrent symptoms (80).

Based on the available evidence, LT modifiers would not be considered sufficient monotherapy for moderate to severe asthma. Children with moderate to severe asthma may require high doses of ICS, which sometimes are not sufficient to control symptoms. Also, some evidence shows that adult patients on high-dose ICS still have signs of ongoing eosinophilic inflammation (81,82). This may indicate that ICS cannot control all aspects of asthma inflammation, including the unchecked release of Cys-LTs. Therefore, add-on therapy such as LABA or LTRAs should be considered before additional increases are made in the doses of ICS for children who remain symptomatic despite moderate use of ICS (83-84). There is a good rationale for positioning LTRAs as complementary to ICS treatment in children whose symptoms are not optimally controlled with a moderate dosage of steroids such as 400µg/day. RCTs should assess the potential of LTRA modifiers as ICS-sparing drugs for children.

EXERCISE-INDUCED ASTHMA

Heat and water loss from the surface of the respiratory tract during exercise leads to hyperosmolar stimulation of mast cells which degranulate and release mediators of bronchoconstriction. Compounds which stabilize mast-cells or which antagonize the mediators they release have the potential to prevent EIA. Cys-LTs are released from a range of inflammatory cells, notably mast cells and EOS, and have been implicated in the pathogenesis of exercise-induced airway obstruction. An increase in LTE4 has been observed after exercise in adults and in children with severe asthma (85), although neither the pre-exercise LTE4, nor the rise in LTE4 after exercise correlated with the degree of exercise-induced bronchoconstriction (EIB) (86).

Given the social and physical importance of exercise for children's life, (EIB) is one of the most important symptoms to treat from the child's perspective. Two large UK surveys have documented prevalence rates of exercise-related symptoms in 87% (87) and 80% (88) of asthmatic children. Sports that involve outdoor running are those most involved. Structured interviews with preschool children and their parents who were attending a hospital-based asthma clinic found that physical activity caused wheezing in 88% of the children (89). Impairment of activity is also a problem in older children with asthma.

The current guidelines emphasize the use of SABA for EIB. However, children do not have a scheduled life, thus the recommendation to use SABA 15 minutes before exercise is not very realistic for children, as it is for adults. Therefore,

long-term coverage is preferable in children for protection against EIB. LTRAs represent an asthma medication that provide long-lasting bronchoprotection with an antiinflammatory component.

LTRAs taken regularly improve asthma symptoms and lung function in adults and children. In adults they block both early and late reactions to antigen challenge and reduce sputum eosinophilia (44). In asthmatic children they reduce NO in exhaled air (25). Their value in treating asthmatic children with symptoms provoked by physical activity has been assessed by exercise challenge and QoL questionnaire.

The effect of montelukast 5 mg administered once daily on exercise challenge was assessed in 27 children aged 6-14 years with stable asthma in a randomized double-blind placebo-controlled cross-over trial. Six-minute treadmill exercise-challenges were performed 20-24 hours after the last dose in each trial period. Montelukast significantly reduced the area above the FEV1 time curve for 0-60 min after exercise by 60% compared with placebo, the maximum fall in FEV1 (31% inhibition relative to placebo, $p<0.05$), but not the time to recovery (90). Although montelukast did not completely prevent EIB, the results of this study suggest that a single oral dose given in the evening will confer a considerable protection throughout the following day.

A further study examined the impact of montelukast on activity induced symptoms through the use of a QoL questionnaire in children aged 9-14 years, with intermittent or persistent asthma. After the 8-week treatment period the activity domain score improved by a mean of 1.1 for montelukast compared with 0.6 for placebo ($p<0.001$) (91).

No controlled trials have been published in children to describe the impact of long-term treatment with LTRAs on EIB in asthmatic children.

Studies in adults suggest that tolerance and loss of protective effect do not occur. In a recent adult study, the degree of inhibition of EIB in patients aged 15-45 years was consistent over 12 weeks of continuous treatment with montelukast 10 mg daily, without development of tolerance, with return to baseline exercise response values two weeks after cessation of treatment (37). In adults, but not in children, montelukast was compared to salmeterol with regard to the capacity to give sustained protection against EIB. After initial equivalent protection, a greater protection was afforded by LTRA after 4 and 8 weeks, due to the development of tolerance with long-term use of salmeterol (49).

A study involving about 300 families showed that montelukast taken once daily was preferred by children and parents and compliance was better than with four time daily inhaled cromolyn (92). In conclusion, LTRAs administered once daily provide protection throughout the 24 hours with no tolerance in the long term, ensuring improvement in activity-related QoL.

ASPIRIN-SENSITIVE ASTHMA

Aspirin-sensitive asthma (ASA) is caused by a specific mechanism present in a minority of asthmatic patients. This mechanism is poorly understood but may be due to shunting of the AA substrate from the cyclo-oxygenase (CO) pathway to the 5-LO pathway, up-regulating the Cys-LTs pathway. Cys-LTs inhibition seems particularly effective in patients with ASA. LTRAs resulted in almost complete inhibition of aspirin-induced bronchocostriction, as well as symptoms of the skin and gastrointestinal tract (93-94).

In order to examine the effects of LTRAs on aspirin challenge on eosinophil activity and chemical mediators released into the airway of asthmatic children, oral provocation test with aspirin was performed in aspirin-intolerant asthmatic patients and aspirin tolerant asthmatic patients. In ASA, aspirin induced an immediate reaction characterized by increased urinary LTE4/Cr and sputum eosinophil cationic protein (ECP), and a fall in urinary 11-dehydrothromboxane/Cr (11-dhTXB2/Cr). Pranlukast inhibited the bronchial reaction and increased the sputum ECP after threshold doses of ASA, but failed to change aspirin-induced LT production in sputum and urine. In AIA, aspirin challenge was only associated with a fall in urinary 11-dhTXB2 (95). Therefore, LTRAs are useful for AIA through inhibition of LTs production and eosinophilic inflammation in the airway.

CONCLUSIONS

Most of the long-term experience in treating children with asthma is with ICS. However, these

agents are not without disadvantages. In this regard, the LTRAs offer distinct advantages, mainly the convenience of oral delivery and a more favourable tolerability profile. These properties, coupled with the fact that the LTRAs provide effects additive to those of ICS and permit long-term reduction in ICS dosage, suggest that LTRAs are an attractive option for complementary therapy in patients with chronic persistent symptoms who have a suboptimal response to low-to- moderate doses of ICS and who show poor compliance to this therapy. Indeed, the NAEPP (1) and some International (96) guidelines already include LTRAs in their recommendations for managing asthma. In the author's UK-based practice, montelukast is used as "add-on" therapy to allow tapering of ICS dose and reduce ß-agonist requirements. Because of greater safety and lack of tolerance to the effects of this LTRAs, montelukast is added in preference to increasing ICS dose or adding a LABA. There is a temptation to employ LTRAs as therapy in children also for first-line prophylaxis in mild-persistent asthma, this approach being recommended in the US (1) and some international therapeutic guidelines (50); although, in the absence of further published trial evidence, this approach has not yet been fully accepted.

In summary, based on the present published trial evidence, LTRAs have utility in a number of circumstances in asthma: as first-line treatment in young wheezing pre-school children with mild recurrent symptoms; in asthmatic school children monotherapy with LT modifiers cannot sufficiently control moderate to severe asthma, and their efficacy in mild asthma has not been studied; as complementary treatment to be added to ICS in asthmatic school children; in ASA and EIB; in adults, as add-on therapy to regulate ICS (98-114).

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