

The role of leukotriene receptor antagonists in the treatment of chronic asthma in childhood

A considerable increase in the prevalence of childhood asthma over the last few decades has been mirrored by a dramatic increase in usage of anti-asthma drugs; however, there has been no reduction in the numbers of patients dying of asthma. Concern has been expressed about the development of tolerance with continuous use of inhaled β -agonist bronchodilators and about the potential adverse systemic effects of high-dose inhaled corticosteroids in children. Moreover, patient compliance with inhaled therapy tends to be poor. The leukotriene receptor antagonists, including montelukast, pranlukast and zafirlukast, are orally administered agents with proven benefits in asthma. In a large, placebo-controlled pediatric trial, montelukast significantly ($P < 0.02$) reduced requirements for rescue β -agonist bronchodilators, improved quality of life, reduced the circulating level of blood eosinophils and produced improvements in lung function. In adult studies, montelukast reduced sputum eosinophils and attenuated early and late phase allergen-induced reactions. Montelukast has also demonstrated protective effects against exercise-induced bronchospasm in both adults and children, and this protection was maintained during the trough period at the end of the once-daily administration interval (namely, 20–24 h post-dose). Several studies have demonstrated that the formation of cysteinyl leukotrienes in the airways of asthmatic patients is not suppressed by corticosteroids; thus, it is not surprising that montelukast demonstrates complementary effects when given with inhaled corticosteroids. Currently, the most compelling evidence from published trials suggests that leukotriene receptor antagonists can be used as add-on therapy to inhaled corticosteroids to allow tapering of corticosteroid dose and reduction in β -agonist use. Recent clinical trial results suggest there may also be a role for these agents as first-line therapy in children with mild asthma.

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The prevalence of childhood asthma has increased over the past few decades, as have hospitalizations for the disease (1–3). These increases have been mirrored by a dramatic rise in the use of anti-asthma drugs. While there has been little decrease in asthma deaths among children 5–15 years of age, the risk of a patient dying of asthma has decreased. However, 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 (4). Moreover, there is no evidence that any therapeutic intervention modifies the natural history of the disease. Those with mild episodic asthma retain normal lung function even after 28 years of follow-up (5), while those with persistent disease in adulthood have lower lung function and increased airway hyperresponsiveness at the outset (6). In neither of these two extremes has the use of inhaled corticosteroids appeared to have any influence.

The two classes of drugs most commonly used for

treating childhood asthma, namely the β -agonist bronchodilators and inhaled corticosteroids, have both come under increasing scrutiny in the last few years. The development of tolerance resulting from continuous use of β -agonists is of concern, as is the risk of adverse systemic effects with inhaled corticosteroids, particularly in children requiring high dosages. In addition, ensuring adequate compliance with inhaled therapy continues to be a major difficulty. Against this 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.

Problems with inhaled corticosteroid therapy in children with asthma

Current national and international guidelines for managing childhood asthma (7–9) emphasize the

important role of inhaled corticosteroids. This has been a consequence of improved insights into the immunopathology of the disease. Many studies in adults have shown that eosinophilic bronchitis underlies the condition, even in its milder forms (10). These insights can now be extended to children, with several studies showing a predominance of eosinophilic inflammation in young asthmatics (11, 12). Inhaled corticosteroids are usually introduced when intermittent inhaled β -agonist bronchodilators 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 (7). However, some children fail to respond to this therapy. The most common reason for the apparent resistance to inhaled corticosteroids is lack of compliance with inhalations (7, 13). Young children, in particular, often experience delivery and technique problems with both pressurized metered-dose inhalers and dry powder inhalers, even when supervised by an adult.

These drug delivery problems in children are often superimposed on suboptimal understanding of the nature of asthma and the concept of inhaled corticosteroid therapy, a problem seen in adults as well as children. In a drug utilization study, 33% of patients who were prescribed regular inhaled corticosteroids were found to be using them on a "prn" (as required) basis (14). In another study, compliance rates with inhaled corticosteroids were significantly less ($P < 0.001$) than those with oral theophylline (15). These findings suggest that patients usually prefer the oral route of administration over other routes; the reasons for this preference are uncertain but may relate to social or psychological discomfort (16). Patients also prefer less complicated regimens: the more complicated the schedule (in terms of frequency of administration), the less the degree of compliance (17, 18).

Because compliance is an important factor affecting the success of anti-asthma therapy (13, 19) these findings, coupled with frequently poor inhaler technique among children, may explain the difficulties faced by clinicians in ensuring adherence to their instructions for administering inhaled corticosteroids. Although much can be achieved with asthma educational programs, newer anti-asthma drugs that (a) provide equivalent or greater efficacy than inhaled corticosteroids and (b) can be given orally and in simplified once-daily regimens appear to hold great promise for improving adherence to prescribed treatment.

Potential adverse systemic effects of inhaled corticosteroids

In addition to the problem of compliance, the potential of inhaled corticosteroids to cause adverse systemic effects in children, particularly at high dosages, is another factor giving rise to concerns about their use. The main areas of concern centre around possible

effects on the hypothalamic–pituitary–adrenal axis, growth and bone metabolism and density (possible increased risk of osteoporosis). Low doses of inhaled corticosteroids ($< 400 \mu\text{g/day}$) are not normally associated with evident systemic effects in children; however, the risk of such adverse effects increases when doses $> 800 \mu\text{g/day}$ are needed to control asthma symptoms. In particular, significant inhibitory effects on short-term and intermediate-term growth have been reported with high dosages of inhaled corticosteroids (20, 21). In children with very mild asthma, there may even be an effect on growth with doses of inhaled corticosteroids as low as $400 \mu\text{g/day}$ of beclomethasone dipropionate or equivalent (22). Furthermore, it has clearly been shown that, at $400 \mu\text{g/day}$, there is a consistent effect on nocturnal cortisol profiles and morning urinary free cortisol, which demonstrates that there is a systemic effect even of moderately low doses (23). What impact this has clinically in the medium and long term has yet to be elaborated. However, there remains a lingering concern that decades of treatment with inhaled corticosteroids, particularly from early childhood, might have an impact on calcium accumulation in bone that will show itself only in later adult life with early osteoporosis and susceptibility to fractures (24).

For these reasons, physicians have become reluctant to increase the dose of inhaled corticosteroids in children, and other strategies should be considered when there is evidence that control of asthma is not optimal. One such strategy is to use a long-acting β -agonist bronchodilator to reduce the required inhaled corticosteroid dosage. Adult studies assessing the effects of adding long-acting β -agonist to inhaled corticosteroids, compared with a doubling of corticosteroid dose, have shown benefits in terms of improved lung function and symptom control (25, 26). However, hitherto, studies in children have not shown this to the same extent. In a 1-year study of 177 children no additional benefit was gained from adding salmeterol to a moderate dose of inhaled beclomethasone ($400 \mu\text{g}$ daily) or, indeed, from doubling the dose of the corticosteroid to $800 \mu\text{g}$ daily (27). Moreover, this approach may be complicated by the development of tolerance to the β -agonist, as has been reported with salmeterol in adolescents with exercise-induced asthma (28).

Characteristics of the ideal drug for treating childhood asthma

In light of these concerns regarding current management of childhood asthma, the ideal drug for treating asthma in children may be defined as one that:

- is orally active to encourage optimal medication compliance;

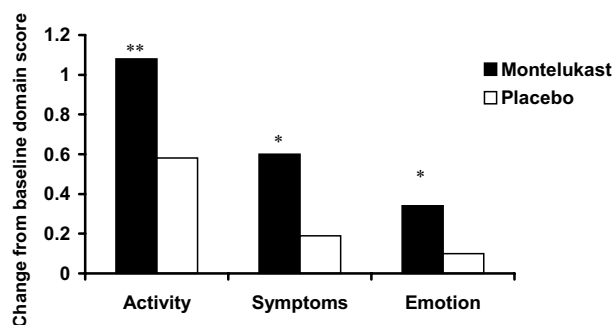


Figure 1. Change from baseline in quality-of-life domain scores (recorded on a seven-point scale ranging from 1=worst to 7=best) after 8 weeks of treatment in 336 children aged 6–14 years with chronic asthma who received either montelukast or placebo in a randomized, double-blind trial (48). Change from baseline significantly greater for montelukast versus placebo: * $P \leq 0.007$; ** $P < 0.001$.

- has a long duration of action, requiring less frequent administration;
- has anti-inflammatory and disease-modifying properties as well as bronchodilator effects to improve symptoms;
- has beneficial effects on other atopic manifestations commonly associated with asthma, such as allergic rhinitis and atopic dermatitis; and
- has a favourable tolerability profile, both in infants and older children.

Leukotriene receptor antagonists for managing childhood asthma

Overview of leukotriene receptor antagonists and their effects in treating asthma

After the discovery in the late 1970s that the cysteinyl leukotrienes LTC_4 and LTE_4 (formerly known collectively as the slow-reacting substance of anaphylaxis [SRS-A]) play a key role in the pathophysiology of asthma (29, 30) a number of specific antagonists of their actions have been developed. The leukotriene receptor antagonists (LTRAs), including montelukast, zafirlukast and pranlukast, selectively block the binding of cysteinyl leukotrienes to the CysLT_1 receptor, which has been identified as the receptor through which most of their actions are mediated. These actions include bronchoconstriction, mucus hypersecretion and increased vascular permeability and eosinophil migration (29). Consequently, the LTRs inhibit bronchoconstriction (30). Moreover, LTRAs prevent many types of provoked asthmatic responses, including allergen-induced, exercise- and cold air hyperventilation-induced, and aspirin-induced asthma (29, 30).

In clinical studies across diverse patient subgroups, montelukast, zafirlukast and pranlukast are effective when given orally in improving symptom control and

airway function in patients with chronic persistent asthma as well as in decreasing the frequency of exacerbations requiring oral corticosteroids (29, 31–34). The LTRAs produce bronchodilator effects that are additive to those of β -agonists and decrease requirement for use of these drugs (29, 35).

In recent studies, montelukast has shown similar activity to that of an inhaled corticosteroid for controlling asthma in adults (36) and provided additional control in patients incompletely controlled on an inhaled corticosteroid (37). Moreover, the dose of inhaled corticosteroid may be decreased while maintaining control of asthma for adult patients receiving once-daily oral montelukast (38) or twice-daily pranlukast (39). This is probably because of complementary anti-inflammatory effects, as corticosteroids do not suppress the formation of cysteinyl leukotrienes in asthma. This observation was demonstrated in a study in which prednisone treatment did not suppress the formation of cysteinyl leukotrienes in bronchoalveolar lavage fluid of patients with asthma (40). Furthermore, similar observations have now been made *in vitro* in relation to children who wheeze. Bronchoalveolar lavage macrophages harvested from infant wheezers, when appropriately stimulated, produce far higher levels of cysteinyl leukotrienes than those harvested from non-wheezers. However, the production of cysteinyl leukotrienes was not inhibited by coculturing the macrophages with ever-increasing doses of dexamethasone (41). Moreover, there was no suppression of the allergen-induced increase in LTE_4 urinary excretion after administration of inhaled fluticasone to patients with asthma (42).

As well as their additive effects with β -agonists and inhaled corticosteroids, the LTRAs may also produce an additive effect with H_1 -antihistamines in inhibiting allergen-induced early and late phase airway obstruction.

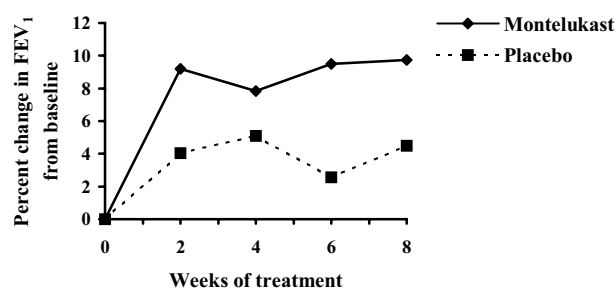


Figure 2. Effects of montelukast and placebo on morning FEV_1 (mean percentage change from baseline) over 8 weeks in a randomized, double-blind trial enrolling 336 children aged 6–14 years with chronic asthma (48). No loss of effect of montelukast was evident over the 8-week period (mean change during treatment, $P < 0.001$ for comparison with placebo). Reproduced with permission from Knorr et al. (48).

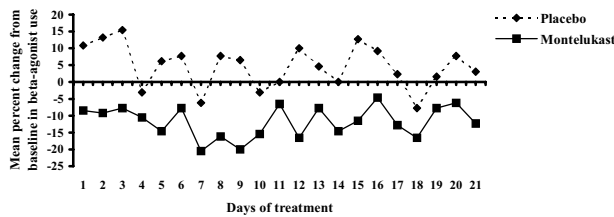


Figure 3. Time-response profile showing effects of montelukast and placebo on as-needed daily inhaled β -agonist bronchodilator use (mean percentage change from baseline) during the first 21 days of therapy in a randomized, double-blind trial enrolling 336 children aged 6–14 years with chronic asthma (48). The difference in mean values after the first dose between the montelukast and placebo groups was statistically significant ($P=0.02$). Reproduced with permission from Knorr et al. (48).

tion in asthmatics (43, 44). However, this possibility remains to be demonstrated in long-term clinical trials.

Results of clinical trials with montelukast in childhood asthma

In the United States, montelukast and zafirlukast are approved for use in children, montelukast for children 2 years and older and zafirlukast for children 7 years and older. Montelukast has the longest duration of effect, which persists throughout the once-daily dosage interval. In contrast, zafirlukast and pranlukast are both given twice daily.

Montelukast produces significant improvements in quality of life and measures of lung function in both adult and paediatric patients with chronic asthma, irrespective of the use of inhaled corticosteroids, and has a tolerability profile similar to that of placebo (32, 45–47). In a multicentre, double-blind controlled trial in which montelukast (5 mg once daily) was compared with placebo in 336 asthmatic children aged 6–14 years, both the percentages of days, and of patients, with asthma exacerbations were significantly lower in the group receiving montelukast ($P=0.049$

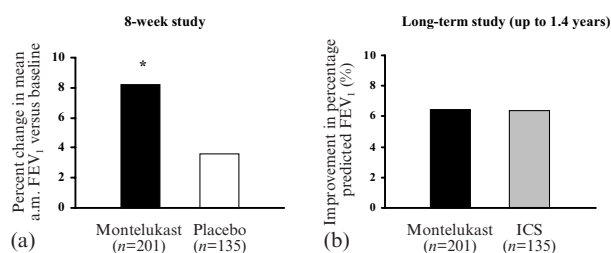


Figure 4. Changes in FEV_1 values in: (a) the 8-week, randomized, double-blind trial of montelukast versus placebo enrolling 336 children aged 6–14 years with chronic asthma (48) and (b) the long-term, open-label extension trial of montelukast versus inhaled corticosteroid therapy in 239 children (49). Patients in the long-term study were treated with montelukast for up to 1.4 years. * $P<0.05$ versus placebo. ICS=inhaled corticosteroid.

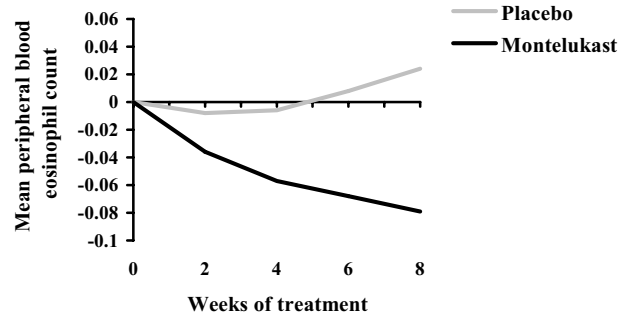


Figure 5. Reduction in mean peripheral blood eosinophil counts (mean number of cells $\times 10^9/L$) in the montelukast and placebo treatment groups in a randomized, double-blind trial enrolling 336 children aged 6–14 years with chronic asthma (48). The reduction versus placebo was statistically significant over the 8-week treatment period ($P=0.02$). Reproduced with permission from Knorr et al. (48).

and $P=0.002$, respectively, vs. placebo) (48). As shown in Fig. 1, asthma-specific quality of life parameters improved with montelukast. The change from baseline in the montelukast group was significantly greater ($P\leq 0.007$) than that in the placebo group for the three quality-of-life domains assessed (activity, symptoms, and emotions) after 8 weeks of treatment. The most marked difference vs. placebo was in the activity domain ($P<0.001$). Fig. 2 illustrates the effect of montelukast on morning forced expiratory volume in 1 s (FEV_1) over time. Significant and consistent improvements over the 8-week treatment period ($P<0.001$) were observed compared with placebo. The onset of action of montelukast, as reflected in the requirement for β -agonist bronchodilators over the first 3 weeks of treatment, was rapid and was seen within 1 day of starting therapy (Fig. 3).

In a subsequent open-label extension of this study, in which children received either montelukast or an inhaled corticosteroid for periods of up to 1.4 years, the improvement in percentage of predicted FEV_1 values with montelukast was maintained, and the change from baseline was similar to that in the inhaled corticosteroid group (6.5% and 6.4%, respectively) (49), as shown in Fig. 4. These findings suggest that tolerance does not develop to the effect of montelukast.

A beneficial effect of montelukast (5 mg once daily) has also been demonstrated in children with exercise-induced asthma. In a multicentre, double-blind, crossover study in children aged 6–14 years, montelukast provided significant protection ($P\leq 0.05$) against the post-exercise fall in FEV_1 at 20–24 h after a dose of 5 mg (namely, at the end of the dosing interval) and decreased ($P=0.079$) the time to recovery vs. placebo (50). In a recent adult study (51), protection by montelukast against exercise-induced bronchoconstriction was consistent over 12 weeks, without

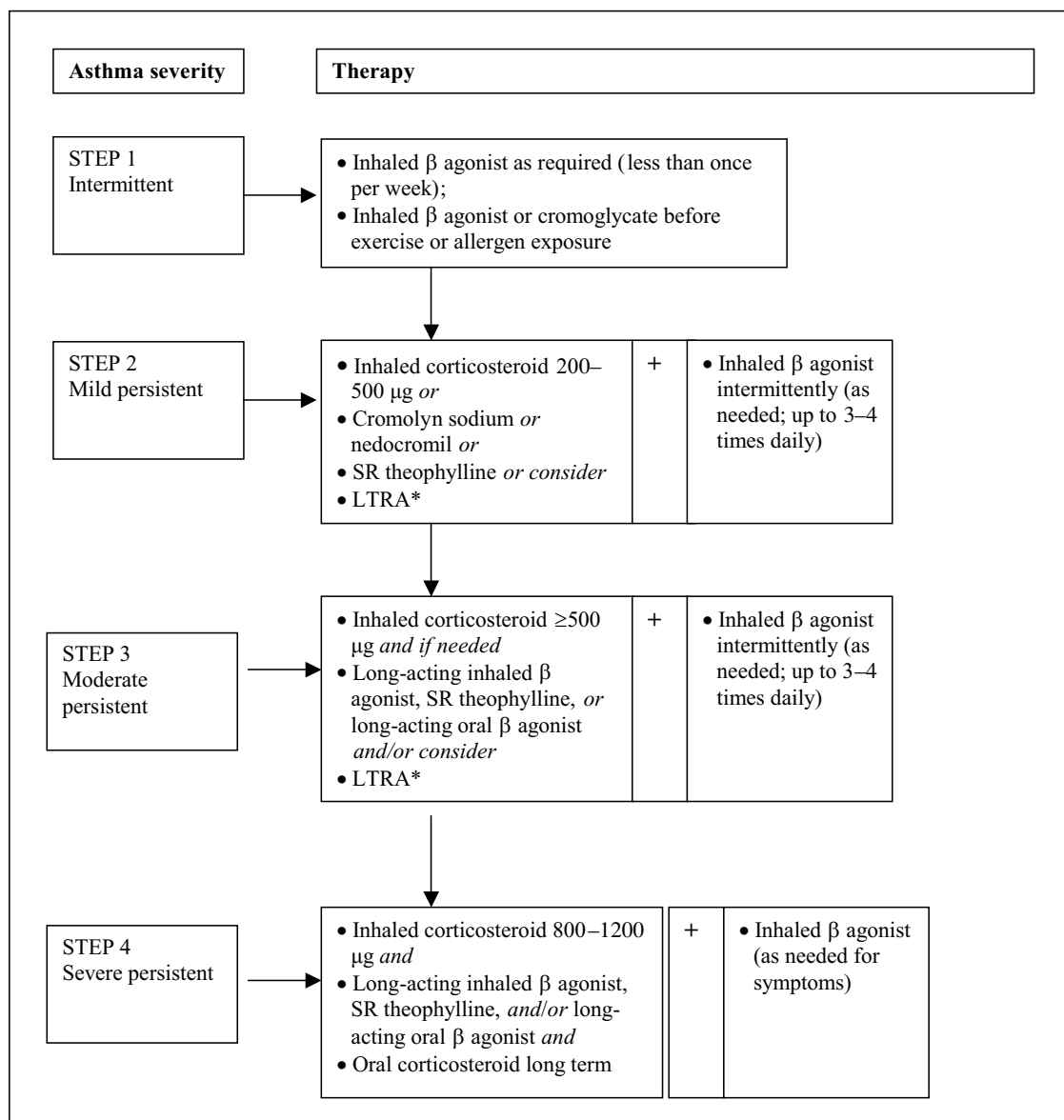


Figure 6. Therapeutic algorithm for management of asthma in adults and children over 5 years old, indicating the current place of leukotriene receptor antagonists (LTRAs), as outlined in the GINA Pocket Guide for Asthma Management and Prevention (59). SR theophylline, sustained-release theophylline. *Use of LTRA as first-line therapy in Step 2 is an alternative proposed in these and the US therapeutic guidelines (8, 59) although, in the absence of further published trial evidence, this approach has not yet been fully accepted.

development of tolerance. This finding is particularly relevant for children, who tend to be active at frequent and irregular intervals throughout the day.

Influence of leukotriene receptor antagonists on eosinophils

Eosinophils play an important role in asthmatic inflammation. In the 8-week double-blind, placebo-controlled paediatric trial (48), treatment with montelukast caused a significant decrease ($P=0.02$) in peripheral blood eosinophil counts in comparison with placebo during the active treatment period (Fig. 5), suggesting that montelukast may have clinically relevant effects on asthmatic inflammation. In a recent study in adult patients with chronic asthma, montelukast caused

a decrease in blood eosinophil levels that was similar to that caused by inhaled beclomethasone (52). In other adult studies, eosinophilic inflammation in the airways of patients with asthma was reduced by treatment with montelukast or pranlukast (53–55). Pizzichini and coworkers (53) found that double-blind treatment for 4 weeks with montelukast (10 mg once daily) reduced sputum eosinophils significantly more ($P=0.026$) than placebo. Treatment with pranlukast for 4 weeks significantly reduced ($P<0.05$), compared with placebo, the number of activated eosinophils on bronchial biopsies from patients with mild to moderate asthma (54). Bronchial biopsies were used also in a second double-blind study of montelukast, in which the numbers of chromotrope 2R-positive cells, a marker

for the total number of eosinophils, were significantly reduced ($P < 0.05$) from baseline after 6 weeks of treatment with montelukast; the change from baseline in the placebo group was not statistically significant (55).

Tolerability findings

Montelukast was well tolerated in the 8-week randomized, controlled paediatric trial (48). Interestingly, the only significant difference ($P = 0.01$) between the montelukast and placebo treatment groups was the lower incidence of allergic rhinitis among montelukast-treated patients. Similarly, in adult trials, clinical and laboratory adverse experiences were similar for patients receiving montelukast or placebo (46).

Churg–Strauss syndrome, or allergic granulomatous vasculitis, has been reported in patients receiving anti-asthma therapy, including LTRAs as well as salmeterol and inhaled corticosteroids, most commonly when oral corticosteroids are tapered because of the addition of new anti-asthma therapy (56, 57). The exact mechanism resulting in Churg–Strauss syndrome is unclear; however, affected patients most likely have an underlying eosinophilic disorder that is unmasked by systemic corticosteroid withdrawal (58). Therapy with LTRAs or inhaled corticosteroids is unlikely to be the direct cause. Churg–Strauss syndrome is extremely rare in children.

Conclusions: current place of leukotriene receptor antagonists in childhood asthma

Most of our long-term experience in treating children with asthma is with inhaled corticosteroids; however, these agents are not without disadvantages, most notably (a) the fact that they do not block the release of cysteinyl leukotrienes in asthma; (b) their potential for adverse effects on growth and skeletal development when used in high doses in children; and (c) difficulties in achieving adequate compliance with their use. In this regard, the LTRAs offer distinct advantages – in particular, the convenience of oral

delivery and a more favourable tolerability profile. These properties, coupled with the fact that LTRAs produce effects additive to those of inhaled corticosteroids and permit long-term reductions in corticosteroid 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 inhaled corticosteroids or who are poorly adherent to this therapy. Indeed, both US (8) and some international (59) guidelines already include LTRAs in their recommendations for managing asthma, and the current place of these drugs in childhood asthma is defined in the therapeutic algorithm in Fig. 6.

In the author's UK-based practice, montelukast is used as "add-on" therapy to allow tapering of inhaled corticosteroid dose and reduce β -agonist requirements. Because of greater safety and lack of tolerance to the effects of this LTRA, montelukast is added in preference to increasing corticosteroid dose or adding a long-acting β -agonist. There is a temptation to employ LTRAs as therapy in children also for first-line prophylaxis. Certainly, this approach has been recommended in US and some international therapeutic guidelines (8, 59) although, in the absence of further published trial evidence, this approach has not yet been fully accepted worldwide.

Results of long-term clinical trials of the efficacy of LTRAs as prophylaxis in children with asthma will better guide our use of these agents for treating childhood asthma. Nevertheless, it is apparent that the LTRAs offer a new and substantially different therapeutic option in childhood asthma, and one that is potentially very valuable in the overall management of this disorder.

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