Clinical Medicine Reviews in Therapeutics

Montelukast Sodium: Administration to Children to Control Intermittent Asthma

Cornelia M. Gravett[1], Gregory R. Tintinger[1,2], Annette J. Theron[1], Ronald Anderson[1], Charles Feldman[3] and Robin Green[4]

[1]Medical Research Council Unit for Inflammation and Immunity, Department of Immunology, Faculty of Health Sciences, University of Pretoria, and Tshwane Academic Division of the National Health Laboratory Service, Pretoria, South Africa. [2]Department of Internal Medicine, Steve Biko Academic Hospital, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa. [3]Division of Pulmonology, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa. [4]Department of Paediatrics, Steve Biko Academic Hospital, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.
Correponding author email: corlig@iafrica.com

Abstract: The prototype cysteinyl leukotriene receptor antagonist, montelukast, is generally considered to have a niche application in the chemotherapy of exercise-induced asthma. It has also been used as add-on therapy in patients whose asthma is poorly controlled with inhaled corticosteroid monotherapy, or with the combination of a long-acting β(2)-agonist and an inhaled corticosteroid. Recently, however, montelukast has been reported to possess secondary anti-inflammatory properties, apparently unrelated to conventional antagonism of cysteinyl leukotriene receptors. These novel activities enable montelukast to target eosinophils, monocytes, and, in particular, the corticosteroid-insensitive neutrophil, suggesting that this agent may have a broader spectrum of anti-inflammatory activities than originally thought. If so, montelukast is potentially useful in the chemotherapy of intermittent asthma because most exacerbations of this condition involve respiratory virus infection-triggered inflammatory mechanisms which, to a large extent, involve airway epithelial cell/neutrophil interactions. The primary objective of this review is to evaluate the role of montelukast in the treatment of intermittent asthma in children.

Keywords: airway epithelial cells, corticosteroids, inflammation, neutrophils, respiratory viruses, virus-induced wheeze

Clinical Medicine Reviews in Therapeutics 2010:2 1–10

This article is available from http://www.la-press.com.

Introduction

About 300 million of the world's population is affected by asthma,[1] which is the most common chronic disease in children. By definition "asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airway obstruction, that is often reversible either spontaneously or with treatment".[2] In children, especially those younger than five years of age (pre-school), the diagnosis and treatment of asthma may be challenging. Children are often excluded from clinical trials of available treatments, while lung function tests are difficult or impossible to perform. Furthermore, published reports often do not distinguish asthma from other causes of wheezing.

Although the new GINA guideline no longer focuses on asthma severity, but rather targets asthma control,[2] the initial assessment and treatment plan of the patient will be guided by symptom severity and a consideration of whether the asthma is persistent or intermittent. The four categories of asthma stated are: i) intermittent; ii) mild persistent; iii) moderate persistent; and iv) severe persistent.

In the case of intermittent asthma in children, acute exacerbations and bronchoconstriction are often followed by lengthy symptom-free periods which persist for several weeks, or even months. The exacerbations are often severe, being triggered by viral infections, exercise, or exposure to allergens, resulting in bronchoconstriction, either in isolation, or together with symptoms of allergic rhinitis. A cautious approach to treatment is necessary in these patients. The need for controller medication in the form of inhaled corticosteroids (ICS), oral corticosteroids, or leukotriene receptor antagonists (LTRAs) has been advocated in a number of studies.[3,4] In the GINA guideline, the use of LTRAs is recommended either as an alternative controller therapy to ICS in mild persistent asthma, or as add-on therapy to other controller medications in patients with moderate-to-severe asthma.[2] The Paediatric Consensus Report (PRACTALL)[5] identifies specific paediatric indications for the use of LTRAs as monotherapy. Montelukast is the only LTRA approved for use in the paediatric age range.

In this review, our primary objective is to evaluate the role of montelukast in the treatment of intermittent (episodic) asthma in children, with emphasis on mode of therapeutic action, metabolism and pharmacokinetics, safety, and efficacy. Of necessity, this is preceded by a consideration of the clinical spectrum and underlying inflammatory mechanisms associated with intermittent asthma.

Clinical Spectrum and Inflammatory Mechanisms in Intermittent Asthma

The clinical manifestations of intermittent asthma in children include recurrent episodes of cough, wheezing or dyspnea. However, asthma must be distinguished from numerous other causes of episodic cough or wheezing[6] (Table 1) as the therapy and outcome of these conditions may vary. Of these, viral-induced wheezing (VIW) is important, especially in pre-school children who are at high risk for recurrent viral infections of the upper and lower airways.

Mild intermittent asthma, although characterized by infrequent symptoms and normal lung function, is associated with chronic airway inflammation which may result in irreversible airflow limitation if left unattended.[7] In contra-distinction to VIW, airway inflammation in intermittent asthma is characterized by the presence of eosinophils, macrophages, and T-lymphocytes, compatible with eosinophilic inflammation.[8] However, the eosinophils are fewer in number and are in a less activated state than those in the airways of individuals with persistent asthma.[8] Allergen exposure, understandably, is a trigger for asthma attacks in children with intermittent asthma.

Table 1. Differential diagnosis of episodic cough or wheeze in children.

Viral-induced wheezing
Cystic fibrosis
Tracheomalacia
Purulent bronchitis
Rhinosinusitis
Gastro-esophageal reflux disease
Vocal cord dysfunction or paralysis
Subglottic stenosis
Foreign body aspiration

However, respiratory virus infection is the major precipitant of acute exacerbations in this group.[9]

Viral infections have been implicated not only as triggers of acute asthma exacerbations, but also as inducers of the persistent airway inflammation typical of asthma. In contra-distinction to allergen-induced (atopic) asthma, bronchial epithelial cells, which are the primary targets of viral infection and replication, appear to initiate the airway inflammation responsible for acute exacerbations of intermittent asthma. Following exposure to respiratory viruses, these cells produce an array of pro-inflammatory chemokines/cytokines and bioactive lipid mediators such as leukotrienes (LT) B_4 and C_4.[9] These, in turn, recruit neutrophils, eosinophils, mast cells, monocytes, B-cells and T-cells to the airways, intensifying airway inflammation.[9]

It is now apparent that bronchial epithelial cells and neutrophils are critically involved in causing the airway inflammation triggered by respiratory virus infection. Importantly, both cell types are relatively resistant to the anti-inflammatory actions of corticosteroids, with, in the case of bronchial epithelial cells, resistance being potentiated by hypoxia.[10] The production of IL-17A by airway Th17 cells may also favor superimposition of neutrophilic on eosinophilic inflammation. This cytokine has been reported to trigger the production of the potent neutrophil chemoattractant, IL-8, by human rhinovirus-infected bronchial epithelial cells in the setting of down-regulation of production of the eosinophil chemoattractant, RANTES.[11] Interestingly, children with idiopathic neutropenia appear to be protected from the development of recurrent episodes of wheezing.[12]

Similar corticosteroid-insensitive, pro-inflammatory mechanisms appear to underpin respiratory virus infection-associated bronchiolitis and wheeze in non-atopic children,[13] underscoring the importance of effective, neutrophil-directed chemotherapeutic strategies in both conditions. Importantly, as described below, leukotriene receptor antagonists (LTRAs) such as montelukast, have broad-spectrum anti-inflammatory properties, including downregulation of neutrophil pro-inflammatory activity, which suggests that LTRAs may be more appropriate for inflammatory responses that are neutrophil-dependent.

The role of LTRAs in the treatment of intermittent asthma cannot be considered without reference to the types of airway inflammation associated with this form of asthma as discussed above. The cells and their pro-inflammatory mediators which promote airway inflammation in asthma, as well as the effects of montelukast on these are represented schematically in Figure 1. The complexity of cytokine and chemokine interactions during this process probably accounts for the limited success of therapies targeting single mediators which can be overcome by alternative pro-inflammatory pathways. Therefore, broad-spectrum anti-inflammatory agents such as corticosteroids and montelukast are likely to be of much greater benefit. The extended spectrum of anti-inflammatory activity of montelukast depicted in Figure 1 is discussed below.

Mechanisms of Action of Montelukast

Montelukast is a prototype, selective, pharmacological antagonist of type 1 cysteinyl leukotriene receptors (Cys LT_1Rs). These are G-protein-coupled receptors that recognize the CysLTs, LTD_4 and LTC_4/LTE_4 in a decreasing order of affinity.[14] CysLT_1Rs have a relatively restricted occurrence, being expressed on the plasma membrane of structural cells and inflammatory cells. In the case of the former, interaction of CysLTs with CysLT_1Rs on epithelial cells, fibroblasts/myoblasts, smooth muscle cells, and endothelial cells, results in respective increases in the following pro-asthmatic activities: i) mucus secretion and goblet cells; ii) collagen synthesis and release, with implications for airway re-modeling; iii) contractility and proliferation; and iv) vascular permeability and edema.[14]

In the case of inflammatory cells, CysLT_1Rs are expressed on neutrophils, monocytes/macrophages, basophils, mast cells, dendritic cells, B lymphocytes, and $CD4^+$T cells. However, only mast cells, basophils, eosinophils, and to a lesser extent monocytes/macrophages, possess the necessary enzymes for conversion of LTA_4 to CysLTs. Following their interaction with CysLT_1Rs on target cells, CysLTs exacerbate the allergic/inflammatory reaction by: i) recruiting and activating T_H2 cells and eosinophils; ii) increasing the production of reactive oxidant species by neutrophils, eosinophils, and monocytes/macrophages, these oxidants being mediators of vascular permeability and bronchial hyper-reactivity; and iii) inducing the release of proteolytic enzymes such as

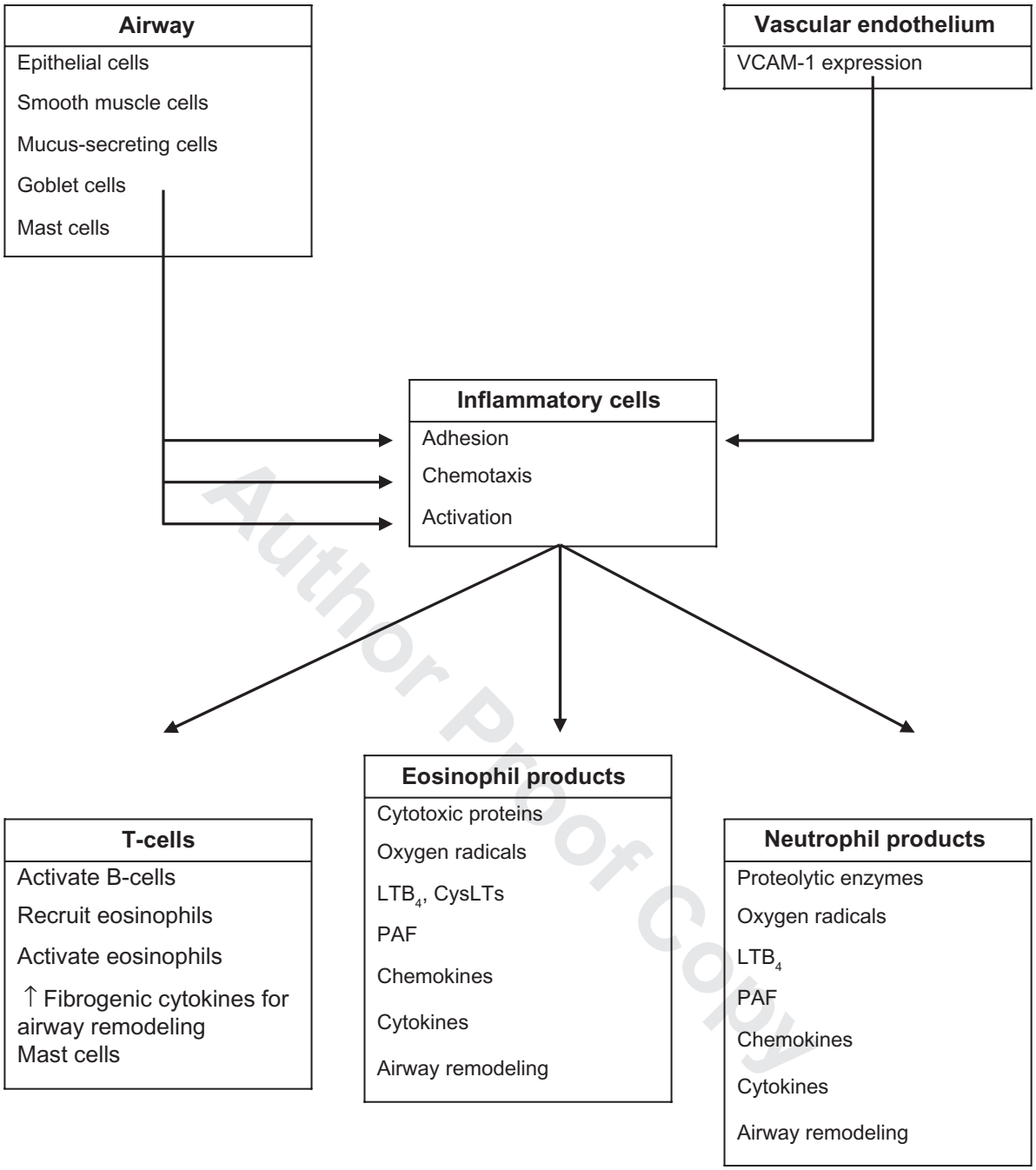

Figure 1. Cells and pro-inflammatory mediators important in the pathogenesis of asthma which are antagonized by montelukast.

elastase and matrix metalloproteinases from phagocytic cells, which in turn promote airway re-modeling.[14–17]

All of these pro-asthmatic/pro-inflammatory activities of CysLTs are effectively antagonized by montelukast, this being the primary mode of therapeutic action of this anti-asthmatic agent. Interestingly, however, several recent studies have revealed that montelukast possesses a range of secondary anti-inflammatory activities, which are apparently unrelated to conventional Cys-LT_1R antagonism. These include the following:

- Inhibition of the enzyme 5-lipoxygenase by a mechanism which has not been fully characterized.[18–20] Importantly, these inhibitory effects of montelukast on 5-lipoxygenase activity in activated neutrophils and monocytes are detectable at pharmacologically

relevant concentrations of this agent and result in decreased synthesis not only of CysLTs, but also of LTB_4, a potent activator of, and chemoattractant for neutrophils, monocytes/macrophages, mast-cells and T cells.[14] Inhibition of synthesis of CysLTs clearly complements montelukast-mediated antagonism of $CysLT_1Rs$, while attenuation of production of LTB_4 represents a potentially important additional therapeutic activity which may contribute to the control of neutrophil-mediated inflammation. It is noteworthy that LTB_4 has been implicated in the development of inflammation in allergic diseases, particularly those which are poorly responsive to corticosteroids in which the neutrophil may be major culprit.[21,22]

- Non-specific inhibition of cyclic nucleotide phosphodiesterases in neutrophils, and presumably other types of immune and inflammatory cells, leading to increased intracellular levels of adenosine 3', 5' cyclic monophosphate (cAMP), which has potent broad-spectrum anti-inflammatory properties.[19] At concentrations which are within, or moderately above the peak therapeutic serum concentrations, montelukast was found to inhibit the production of reactive oxygen species and release of the primary granule protease, elastase, by activated neutrophils by a cAMP-dependent mechanism. Importantly, cAMP has also been reported to inhibit 5-lipoxygenase and LTB_4 synthesis by activated neutrophils,[23] a mechanism which may underpin the inhibitory effects of montelukast on this enzyme.
- Inhibition of the adherence of eosinophils to vascular endothelium by interfering with the interaction of the eosinophil adhesion molecule, $\alpha_4\beta1$, with its counter-receptor, vascular cell adhesion molecule-1.[24] These anti-inflammatory effects of montelukast were detected at therapeutically relevant concentrations of this agent and may restrict eosinophil-mediated inflammation in asthma.

If operative in the clinical setting, these secondary anti-inflammatory properties of montelukast are likely to complement the primary $CysLT_1R$-directed anti-asthmatic/anti-inflammatory activities of this agent by targeting additional inflammatory cell types and their mediators, especially the corticosteroid-resistant neutrophil. Montelukast may therefore possess anti-inflammatory properties which have a broader spectrum than originally thought, making this agent potentially useful in the treatment of intermittent asthma.

Metabolism and Pharmacokinetic Profile

Absorption

Singulair (montelukast), manufactured by Merck (Merck Research Laboratories, Rahway, NJ, USA), is a popular LTRA, however its effectiveness and blood levels may vary between individuals.[25] It is likely that membrane efflux and uptake transporters mediate the absorption of the drug into the systemic circulation following oral administration. The efflux and uptake transporters may be influenced by genetic variability that could contribute to the observed heterogeneity in response.[25] Mougey et al investigated the possible carrier-mediated uptake of montelukast and showed that the permeability of this drug has an activation energy of 13.7 ± 0.7 kcal/mol, consistent with carrier-mediated transport (4 kcal/mole for passive diffusion).[26] A MDCKII cell line expressing OATP2B1, a membrane transport protein, (coded for by the SLCO2B1 gene), displayed significantly increased permeability of montelukast. Genetic variation of this transport protein was associated with variable montelukast plasma concentrations and variable response to treatment in patients with asthma.[26]

Singulair is rapidly absorbed, primarily in the intestine, following oral administration of the drug. According to the manufacturer, the mean peak montelukast plasma concentration is achieved at 3–4 hours after administration of a 10 milligram (mg) film-coated tablet (FCT) to fasted adults, at 2–2.5 hours after administration of a 5 mg chewable tablet to fasted adults, at 2 hours after administration of a 4 mg chewable tablet to pediatric patients 2 to 5 years of age in the fasted state, while the 4 mg granule formulation is bioequivalent to the 4 mg chewable tablet when administered to adults in the fasted state. The mean oral bioavailabilities are 64%, 73%, 63% for those taking the 10 mg film coated tablets, the 5 mg chewable tablet and the 4 mg chewable tablet, respectively.[27]

Distribution

Distribution of montelukast in body tissues and fluids has not been fully characterized. The steady-state volume of distribution of montelukast is 8–11 L. Montelukast is more than 99% bound to plasma proteins. Studies in rats, using radiolabeled montelukast, indicated minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours post-administration were minimal in all other tissues.

Metabolism

Montelukast is extensively metabolized. In studies using therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.[27] *In vitro* studies, using human liver microsomes, indicated that cytochromes P450, 3A4 and 2C9 are involved in the metabolism of montelukast.[28] No significant difference in montelukast metabolism was found between pediatric (ages 6–11) and adult (ages 50–65) subjects.[28] Since montelukast is metabolized by CYP3A4, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP3A4, such as phenytoin, phenobarbital and rifampicin.[27]

Elimination

Biliary excretion is the predominant pathway for the elimination of montelukast and its metabolites. Urinary excretion is insignificant, and thus dose adjustments in renally compromised patients would not be necessary.[29]

Plasma concentrations in adults and children

The maximum plasma concentration (Cmax) after orally administered montelukast at a dose of 10 mg, ranged from 350–385 ng/ml in healthy male and female subjects, while age had little or no effect when the pharmacokinetic profile of the elderly was compared to that of young adults.[30,31] Administration of 4 mg chewable tablets or 10 mg FCT to children aged 2–5 years and adults respectively, resulted in a similar AUCpop (area under the curve), while the respective Cmax values were 471 ng/ml in the children and 283 ng/ml in adults.[32] A study indicated that a single dose of montelukast (4 mg oral granules) administered to children 3–6 months of age[33] yielded systemic exposures similar to those observed in children aged 6–24 months.[34] The respective maximum plasma concentrations were 561.1 ng/ml and 514.4 ng/ml.[33,34] The pharmacokinetic profile of the 6–24 month group on a single 4 mg dose of montelukast oral granules was also compared to that of adults on 10 mg FCT. The AUCpop values were relatively similar in the two groups, while the Cmax values were 279 ng/ml and 514.4 ng/ml in adults and children respectively.[34] Yet another study indicated that a 5 mg chewable tablet administered once daily to children aged 6–14 years with asthma, resulted in a pharmacokinetic profile comparable to that of the clinically effective 10 mg FCT dose in adults.[35]

Dosages

Clinical trials indicated that the recommended daily dosage for the following age groups are: one 10 mg tablet to adults and adolescents 15 years of age and older; one 5 mg chewable tablet for pediatric patients 6 to 14 years of age; one 4 mg chewable tablet or one packet of 4 mg oral granules to pediatric patients 2 to 5 years of age; and one packet of 4 mg oral granules to pediatric patients 6 to 23 months of age.[27]

Safety

The short- and long-term safety profiles of montelukast as a therapeutic agent in children aged 6 months to 14 years have been studied extensively.[33,36–45] Serious adverse events, such as worsening asthma, appear to be rare[46] and all reported patients with drug overdoses recovered without sequelae.[46] Less serious side effects of montelukast occur uncommonly, but may include pharyngitis, dizziness, nausea, headache, diarrhea, fever, abdominal pain and rash.[33,36,41–44] The incidence of adverse events associated with montelukast is comparable to those of other standard therapies for asthma in childhood and in some studies montelukast was equivalent to placebo.[40] Although FDA approval for montelukast has been obtained for children ≥2 years of age, safety data to date suggest that this agent may also be used for younger patients between the ages of 6 months and 2 years.

A recent meta-analysis concluded that the safety profile of montelukast at approved doses was acceptable

and endorsed recommendations to administer this agent to children.[46] Good clinical practice still mandates that appropriate indications should exist for using montelukast in children and monitoring for adverse events should extend for the full duration of therapy. Based on current evidence, montelukast appears to be a safe drug for the pediatric population.

Although previous reports have linked montelukast to Churg-Strauss syndrome[47] and an increased suicide risk in adult patients,[48] no evidence currently available justifies similar concerns for children treated with this agent.

Efficacy and Clinical Trials

Viral-induced wheezing, a predominantly neutrophil-mediated condition, is likely to be responsive to montelukast therapy. Available clinical trials, although of limited number, appear to support this contention as pre-school children with viral infections benefited from a 7 day course of therapy with this agent.[49] Increased production of cysteinyl leukotrienes in VIW may be effectively targeted by montelukast consequent to the well-recognized antagonistic effect of this agent on cysteinyl leukotriene receptors. Patients with intermittent asthma may suffer from viral-triggered exacerbations and LTRAs should be added to corticosteroid therapy for these patients if the initial clinical response is suboptimal.

Inhaled corticosteroids are widely accepted as the mainstay of therapy for children with chronic asthma. However, LTRAs may have a role in intermittent asthma as add-on or second-line therapy for children who do not respond to ICS or who are unable to use these agents. A 12 week, multi-centre, randomized, placebo-controlled, double-blind study evaluated the clinical efficacy of oral montelukast in 689 children 2 to 5 years of age with chronic persistent asthma.[50] Montelukast significantly improved each of the components of the composite symptom score over 12 weeks of treatment. For example, the reduction in the activity limitation score was 40% versus 22% for placebo ($P < 0.001$). During the 12 weeks of therapy, significantly fewer patients receiving montelukast, required corticosteroid rescue therapy to maintain asthma control. An additional study comparing fluticasone to montelukast in preschool children with asthma-like symptoms found both forms of therapy equally effective.[51]

The 'PREVIA' Study[52] was designed to investigate the role of montelukast in preventing asthma exacerbations in children aged 2 to 5 years, with a history of episodic wheezing. Montelukast reduced the rate of asthma exacerbations by 32% ($P < 0.001$), as well as the requirement for oral corticosteroids ($P = 0.024$), compared to placebo.

A study was designed to determine the role of montelukast in children (2–14 years old) with intermittent asthma defined as a history of intermittent asthma with symptom-free intervals.[53] Montelukast or placebo were administered for a minimum of 7 days from the first symptoms of asthma or at the start of an URTI if this usually preceded asthma in that particular child. The montelukast group had 163 unscheduled health care resource utilizations for asthma compared to 228 in the placebo group (odds ratio 0.65; 95% CI, 0.47–0.89). Symptoms were reduced by 14% and days absent from school by 37% ($P < 0.0001$).

A study from Canada was designed to determine whether montelukast added to usual asthma therapy would reduce the number of days with increased asthma symptoms and unscheduled physician visits in children during the usual September (fall) epidemic of asthma exacerbations seen in that country.[54] Entry criteria included: i) 2–14 year olds; ii) physician-diagnosed asthma; iii) requirement for a rescue inhaler during the previous year; and iv) a history of asthma exacerbations associated with viral infections. Patients were instructed to take one tablet (montelukast or placebo) in the evening, commencing on 1st September, in addition to their usual asthma therapy. Children receiving montelukast experienced a 53% reduction in the number of days with increased asthma symptoms compared with placebo (3.9% vs. 8.3%) and a 78% reduction in unscheduled physician visits.

Exercise-induced bronchoconstriction (EIB) may also occur in children with underlying airway inflammation. Exercise is a recognized trigger for bronchoconstriction which is mediated by changes in airway temperature, humidity and osmolarity. Neutrophils and eosinophils are key cells implicated in EIB together with their lipid mediators (CysLTs, LTB_4 and PAF), reactive oxidant species, and proteases,[55] which are released when these inflammatory cells are activated. Montelukast has been shown in numerous clinical trials to effectively control EIB in children.[56,57]

A placebo-controlled, double-blinded, randomized two-period crossover study[58] was conducted in 27 children who had a mean baseline FEV_1 of 87% of predicted values and a maximal fall in FEV_1 of 35% after exercising on a treadmill for 6 min. None of the children was taking any controller medication for asthma. A washout of at least 4 days separated the montelukast 4 mg dose or placebo arms of the crossover study. Exercise challenge was performed 20–24 hr after the last dose of a 2 day treatment period with montelukast. Montelukast significantly attenuated exercise-induced bronchoconstriction, with more rapid return of the FEV_1 to near-basal values.

In a double-blinded, randomised parallel group design study of four weeks in a group of 6–12 year old asthmatic children, montelukast was found to provide significant protection against EIB in asthmatic children over the 4 week period with no tolerance to the bronchoprotective effect.[57]

Patient Preference

Although ICS effectively control asthma, concern has been expressed regarding the negative effects of these agents on the growth of infants and children.[58] Montelukast is unlikely to retard growth and is thus a viable alternative, provided acceptable control of asthma symptoms is achieved. Montelukast may be preferred in those instances where very young children are unable to operate inhaler devices efficiently and parents have the option of an easy-to-administer oral preparation such as montelukast without resorting to systemic corticosteroids.

Place in Therapy

Montelukast has an important role in the management of intermittent asthma in children based on evidence from clinical trials and an appreciation of the broad-spectrum anti-inflammatory properties of this agent. The potential benefits of montelukast in the therapy of children with intermittent asthma may include the following:

- Montelukast has broad-spectrum anti-inflammatory properties, affecting both eosinophilic and neutrophilic-mediated inflammation which may be useful for controlling both asthma[59] and viral-induced airway disorders,[60,61] respectively.
- Many children with asthma have concurrent rhinosinusitis which has been shown to respond to montelukast.[62] Furthermore, effective treatment of upper airway conditions often improves asthma control.
- The ease of oral administration of montelukast may improve compliance in pre-school children.
- Concerns have been expressed regarding the adverse effects of inhaled corticosteroids[58] and for these children montelukast may provide a useful alternative.
- The excellent safety profile of montelukast in children must be considered when weighing the risks and benefits of various therapeutic strategies for asthma.

Conclusions

Montelukast possesses broad-spectrum anti-inflammatory properties which may be particularly useful in down-regulating both neutrophil- and eosinophil-mediated pro-inflammatory activity inherent in the pathogenesis of viral-induced wheeze and asthma, respectively. However, the extended anti-inflammatory spectrum of montelukast has yet to be fully incorporated into both clinical guidelines and personalized medicine for children with inflammatory airway disorders. Future clinical trials should clearly define the optimal indications for this agent in treating acute exacerbations and chronic asthma.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The peer reviewers of this paper report no conflicts of interest. RA is in receipt of research funding from MSD. CG has received payment for talks from MSD, Astra Zeneca, GlaxoSmith Kline, and Sanofi Aventis and has been sponsored for congress travel by MSD. CF and RG are advisory board members for MSD, serve on the speakers bureau for MSD and have received sponsorship for congress travel from MSD. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Masolini M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee repost. *Allergy*. 2004;59:469–78.
2. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31:143–78.

3. Leonard B, Bacharier MD, Brenda R, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allerg Clin Immunol.* 2008;122:1127–35.
4. Horner CC, Bacharier LB. Management approaches in intermittent wheezing in young children. *Curr Opin Allergy Clin Immunol*. 2007;7:180–4.
5. Bacharier LB, Boner A, Carlsen KH, et al. European Pediatric Asthma Group. *Allergy*. 2008;63:5–34.
6. Weinberger MD, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics*. 2007;120:855–64.
7. Van den Toorn LM. Clinical implications of airway inflammation in mild intermittent asthma. *Ann Allergy Asthma Immunol*. 2004;92:589–94.
8. Vignola AM, Chanez P, Campbell A, et al. Airway inflammation in mild intermittent and in persistent asthma. *Am J Respir Crit Care Med*. 1998;157:403–9.
9. Hashimoto S, Matsumoto K, Gon Y, Ichiwata T, Takahashi N, Kobayashi T. Viral infection in asthma. *Allergol Int*. 2008;57:21–31.
10. Charron CE, Chou PC, Coutts DJC, et al. Hypoxia-inducible factor 1alpha induces corticosteroid-insensitive inflammation via reduction of histone deacetylase-2 transcription. *J Biol Chem*. 2009;284:36047–54.
11. Wiehler S, Proud D. Interleukin-17 A modulates human airway epithelial responses to human rhinovirus infection. *Am J Physiol Lung Cell Mol Physiol*. 2007;293:L505–15.
12. Saglani S, Wilson N, Bush A. Should preschool wheezers ever be treated with inhaled corticosteroids? *Semin Respir Crit Care Med*. 2007;28:272–85.
13. Marguet C, Bocquel N, Benichou J, et al. Neutrophil but not eosinophil inflammation is related to the severity of a first acute epidemic bronchiolitis in young infants. *Pediatr Allergy Immunol*. 2008;19:157–65.
14. Peters-Golden M, Henderson WR. Leukotrienes. *N Engl J Med*. 2007; 357:1841–54.
15. Gualano RC, Vlahos R, Anderson GP. What is the contribution of respiratory viruses and lung proteases to airway remodelling in asthma and chronic obstructive pulmonary disease? *Pulm Pharmacol Ther*. 2006;19:18–23.
16. Lagente V, Boichot E. Role of matrix metalloproteinases in the inflammatory process of respiratory diseases. *J Molec Cell Cardiol*. 2010;48:440–4.
17. Theron AJ, Gravett CM, Steel HC, Tintinger GR, Feldman C, Anderson R. Leukotrienes C_4 and D_4 sensitize human neutrophils for hyperreactivity to chemoattractants. *Inflamm Res*. 2009;57:1–6.
18. Ramires R, Caiaffa ME, Tursi A, Haeggström JZ, Macchia L. Novel inhibitory effects on 5-lipoxygenase activity by the anti-asthma drug montelukast. *Biochem Biophys Res Comm*. 2004;324:815–21.
19. Anderson R, Theron AJ, Gravett CM, Steel HC, Tintinger GR, Feldman C. Montelukast inhibits neutrophil pro-inflammatory activity by a cyclic AMP-dependent mechanism. *Br J Pharmacol*. 2009;156:105–15.
20. Woszczek G, Chen LY, Alsaaty S, Nagineni S, Shelhamer JH. Concentration-dependent noncysteinyl leukotriene type 1 receptor-mediated inhibitory activity of leukotriene receptor antagonists. *J Immunol*. 2010;184:2219–25.
21. Barnes PJ. New molecular targets for the treatment of neutrophilic diseases. *J Allergy Clin Immunol*. 2007;119:1055–62.
22. Ohnishi H, Miyahara N, Gelfand E. The role of leukotriene B_4 in allergic, diseases. *Allergol Int*. 2008;57:291–8.
23. Flamand N, Surette ME, Picard S, Bourgoin S, Borgeat P. Cyclic AMP-mediated inhibition of 5-lipoxygenase translation and leukotriene biosynthesis in human neutrophils. *Mol Pharmacol*. 2002;62:250–6.
24. Robinson AJ, Kashanin D, O'Dowd F, Williams V, Walsh GM. Montelukast inhibition of resting and GM-CSF-stimulated eosinophil adhesion to VCAM-1 under flow conditions appears independent of $CysLT_1R$ antagonism. *J Leukoc Biol*. 2008;83:1522–9.
25. Lima JJ. Treatment heterogeneity in asthma: genetics of response to leukotriene modifiers. *Mol Diagn Ther*. 2007;11:97–104.
26. Mougey EB, Feng H, Castro M, Irvin CG, Lima JJ. Absorption of montelukast is transporter mediated: a common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. *Pharmacogenet Genomics*. 2009;19:129–38.
27. Merck Research Laboratory: Data on file. http://www.merck.com/product/usa/pi_circulars/s/singulair/singulair_pi.pdf
28. Chiba M, Xu X, Nishime JA, Balani SK, Lin JH. Hepatic microsomal metabolism of montelukast, a potent leukotriene D_4 receptor antagonist, in humans. *Drug Metab Dispos*. 1997;25:1022–31.
29. Balani SK, Xu X, Pratha V, et al. Metabolic profiles of montelukast sodium (Singulair), a potent cysteinyl leukotriene1 receptor antagonist, in human plasma and bile. *Drug Metab Dispos*. 1997;25:1282–7.
30. 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;3:445–8.
31. Zhao JJ, Rogers JD, Holland SD, et al. Pharmacokinetics and bioavailability of montelukast sodium (MK-0476) in healthy young and elderly volunteers. *Biopharm Drug Dispos*. 1997;18:769–77.
32. Knorr B, Nguyen HH, Kearns GL, et al. Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. *J Clin Pharmacol*. 2001;41:612–9.
33. Knorr B, Maganti L, Ramakrishnan R, Tozzi CA, Migoya E, Kearns G. Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. *J Clin Pharmacol*. 2006;46:620–7.
34. Migoya E, Kearns GL, Hartford A, et al. Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. *J Clin Pharmacol.* 2004;44:487–94.
35. Knorr B, Larson P, Nguyen HH, et al. Montelukast dose selection in 6- to 14-year-olds: comparison of single-dose pharmacokinetics in children and adults. *J Clin Pharmacol*. 1999;39:786–93.
36. Kondo N, Katsunuma T, Odajima Y, Morikawa A. A randomized open-label comparative study of montelukast versus theophylline added to inhaled corticosteroid in asthmatic children. *Allergol Int.* 2006;55:287–93.
37. Harmanci K, Bakirtas A, Turktas I, Degim T. Oral montelukast treatment of preschool-aged children with acute asthma. *Ann Allergy Asthma Immunol*. 2006;96:731–5.
38. Kearns GL, Lu S, Maganti L, et al. Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. *J Clin Pharmacol*. 2008;48:502–11.
39. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Systematic Reviews*. 2006;4:CD003137.
40. Capristo C, Rigotti E, Boner AL. Update on the use of montelukast in pediatric asthma. [Review]. *Allergy Asthma Proc*. 2006;27:312–8.
41. Ostrom NK, Decotiis BA, Lincourt WR, et al. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. *J Pediatr.* 2005;147:213–20.
42. Van Adelsberg J, Moy J, Wei LX, Tozzi CA, Knorr B, Reiss TF. Safety, tolerability, and exploratory efficacy of montelukast in 6- to 24-month-old patients with asthma. *Curr Med Res Opin.* 2005;21:971–979.
43. Spahr JE, Krawiec ME. Leukotriene receptor antagonists—risks and benefits for use in paediatric asthma. *Expert Opin Drug Saf*. 2004;3:173–85.
44. Storms W, Michele TM, Knorr B, et al. Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged ≥ 6 years. *Clin Exp Allergy.* 2001;31:77–87.
45. Grzelewski T, Stelmach I. Exercise-induced bronchoconstriction in asthmatic children: a comparative systematic review of the available treatment options. *Drugs.* 2009;69:1533–53.
46. Bisgaard H, Skoner D, Boza ML, et al. Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extension. *Pediatr Pulmonol.* 2009;44:568–79.
47. Price D. Tolerability of montelukast. *Drugs*. 2000;59:35–42.
48. Philip G, Hustad CM, Malice MP, et al. Analysis of behavior-related adverse experiences in clinical trials of montelukast. *J Allergy Clin Immunol.* 2009; 124:697–8.
49. Bacharier LB, Phillips BR, Zeiger RS, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *Am J Allergy Clin immunol.* 2008;122:1127–35.
50. Knorr B, Franchi LM, Bisgaard H, et al. Montelukast, a leukotriene receptor antagonist for the treatment of persistent asthma in children aged 2–5 years. *Pediatrics*. 2001;108:1–10.
51. Kooi EMW, Schokker S, Boezen HM, et al. Fluticasone or montelukast for preschool children with asthma-like symptoms: Randomized controlled trial. *Pulm Pharmacol Ther*. 2008;21:798–804.

52. Bisgaard H, Zielen S, Garcia Garcia ML, et al. Montelukast reduces asthma exacerbations in 2 to 5 year old children with intermittent asthma. *Am J Respir Crit Care Med.* 2005;171:315–22.
53. Robertson CF, Price D, Henry R, et al. Short-course montelukast for intermittent asthma in children. *Am J Respir Crit Care Med*. 2007;175:323–9.
54. Johnston NW, Mandhane PJ, Dai J, et al. Attenuation of the September epidemic of asthma exacerbations in children: A randomized, controlled trial of montelukast added to usual therapy. *Pediatrics*. 2007;120:702–12.
55. Hilberg T. Eiology of exercise-induced asthma: physical stress-induced transcription. *Curr Allergy Asthma Rep*. 2007;7:27–32.
56. Kemp JP, Dockhorn RJ, Shapiro GG, et al. Montelukast once daily inhibits exercise-induced bronchoconstriction 6–14 year-old children with asthma. *J Pediatr*. 1998;133:424–8.
57. de Benedictis FM, del Giudice MM, Forenza N, Decimo F, de Benedictis D, Capristo A. Lack of tolerance to the protective effect of montelukast in exercise-induced bronchoconstiction in children. *Eur Respir J*. 2006;28:291–5.
58. Szefler SJ. Advances in pediatric asthma in 2009: Gaining control of childhood asthma. *J Allergy Clin Immunol*. 2010;125:69–78.
59. Wahn U, Dass SB. Review of recent results of montelukast use as a monotherapy in children with mild asthma. *Clin Ther*. 2008;30:1026–35.
60. Kim C-K, Choi J, Kim HB, et al. A randomized intervention of montelukast for post-bronchiolitis: effect on eosiniphil degranulation. *J Pediatr*. 2010; 156:749–54.
61. Han J, Jia Y, Takeda K, et al. Montelukast during primary infection prevents airway hyperresponsiveness and inflammation following re-infection with respiratory syncitical virus. *Am J Resp Crit Care Med*. 2010; Epub ahead of print.
62. Nayak A. A review of montelukast in the treatment of asthma and allergic rhinitis. *Expert Opin Pharmacother*. 2004;5:679–86.