

# Clinical effectiveness and safety of montelukast in asthma. What are the conclusions from clinical trials and meta-analyses?

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**Abstract:** Asthma is a common childhood atopic disease associated with chronicity and impaired quality of life. As there is no cure for this disease, treatment relies on avoidance of triggers such as food and aeroallergens, the use of inhaled bronchodilators/corticosteroids and antiallergic or immunomodulating therapies. Inhaled corticosteroids (ICSs) and bronchodilators have been the mainstay. However, in Asia, myths and fallacies regarding Western medicine and corticosteroids are prevalent and lead to nonadherence to treatment. Also, use of traditional and proprietary herbal medicines is popular. In the past decades, a novel class of nonsteroidal immunomodulating montelukasts has become available. This article reviews the evidence for the effectiveness and clinical efficacy of these medications. A number of randomized and controlled trials have been performed over the years. The majority of studies confirm the usefulness of montelukast as monotherapy and add-on therapy to ICS in mild to moderate childhood asthma across all age groups. ICSs are generally superior to montelukasts for asthma management. However, montelukast has a place in the treatment of young children with viral-triggered wheezing diseases, exercise-induced asthma, and in children whose parents are steroid-phobic and find ICS unacceptable.

**Keywords:** cysteinyl leukotriene receptor antagonist, inhaled corticosteroid, randomized control trial, meta analysis

## Introduction

Asthma is a common, complicated chronic disorder of the airways and is characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. The Canadian Asthma Consensus guidelines suggest that asthma should be considered in individuals who present clinically with recurrent symptoms of breathlessness, chest tightness, wheezing or cough, and signs of variable airflow obstruction.<sup>1</sup> Although manifested in the airways, the disease is part of a systemic disease of atopy.<sup>2</sup>

The prevalence of asthma has increased two to three fold over the past three decades in industrialized countries, and there is evidence to suggest that this prevalence continues to increase.<sup>3</sup> Asthma affects 9% to 20% of children and 1% to 3% of adults in the United States and is more prevalent in children who belong to upper socioeconomic classes, smaller family sizes, and families with overzealous hygiene.<sup>4-10</sup> In the People's Republic of China, the prevalence is estimated to be approximately 5%.<sup>11,12</sup> The increase in prevalence may be due to increased access to medical care, improved recognition, better epidemiological reporting, or increased environmental allergens due to industrialization and pollution. Conversely, the hygiene hypothesis postulates that the cause of asthma and allergic diseases is an unusually clean environment. The hypothesis states that exposure

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to bacteria and other immune system modulators is important during development, and missing out on this exposure increases risk for allergy.<sup>13,14</sup> The management of asthma may be suboptimal in Asia because myths and fallacies regarding Western medicine and corticosteroids are prevalent and lead to nonadherence of treatment.<sup>15–19</sup> Also, use of traditional and proprietary herbal medicines for atopic diseases is popular.<sup>20,21</sup> Noncorticosteroid-based medications such as montelukast may play a role in better control for various atopic diseases in some of these cities.<sup>22,23</sup>

## Pathophysiology of airway inflammation

Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity and plays an essential role in the pathophysiology of asthma. Airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in the characteristic pathophysiological features of the disease. These cells include eosinophils,<sup>24–26</sup> mast cells,<sup>27</sup> neutrophils,<sup>28–31</sup> macrophages,<sup>32</sup> T lymphocytes, dendritic cells,<sup>33</sup> and airway epithelial cells.<sup>34</sup>

Subpopulations of lymphocytes, T helper 1 cells and T helper 2 cells (Th2), have distinct inflammatory mediator profiles and effects on airway function. Generation of Th2 cytokines (eg, interleukin [IL]-4, IL-5, and IL-13) accounts for the overproduction of immunoglobulin E (IgE), presence of eosinophils, and development of airway hyperresponsiveness.<sup>35</sup> There is also a reduction in regulatory T lymphocytes that normally inhibit Th2 cells as well as an increase in natural killer cells that release large amounts of T helper 1 and Th2 cytokines.<sup>36–40</sup> Activation of mucosal mast cells releases bronchoconstrictor mediators (histamine, cysteinyl leukotrienes, prostaglandin D<sub>2</sub>).<sup>41–43</sup> Cysteinyl leukotrienes are potent bronchoconstrictors derived mainly from mast cells.<sup>44–50</sup>

IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic diseases and the development and persistence of inflammation. The mast cell has large numbers of IgE receptors that release a wide variety of mediators to initiate acute bronchospasm and proinflammatory cytokines to perpetuate underlying airway inflammation when activated.<sup>41,51–53</sup>

## Implications of inflammation for therapy

The increased understanding of the inflammatory processes in asthma involving cellular and humoral responses

and cysteinyl leukotrienes has been translated into therapies targeted at interrupting processes mediated by the aforementioned inflammatory cells and mediators.<sup>38</sup> Some investigations have yielded promising results, such as the development of leukotriene modifiers and anti-IgE monoclonal antibody therapy.

Therapeutic agents target multiple factors regulating inflammation in asthma and the redundancy of these processes. Clinical studies also indicate that phenotypes of asthma exist which may have very specific patterns of inflammation that require different treatment approaches. Current studies are investigating novel therapies targeted at the cytokines, chemokines, and inflammatory cells farther upstream in the inflammatory process. For example, drugs designed to inhibit the Th2 inflammatory pathway may cause a broad spectrum of effects such as airway hyperresponsiveness and mucus hypersecretion.<sup>54</sup> Further research into the mechanisms responsible for the varying asthma phenotypes and appropriately targeted therapy may enable improved control for all manifestations of asthma and prevention of disease progression. In some patients, persistent changes in airway structure occur, including subbasement fibrosis, mucus hypersecretion, injury to epithelial cells, smooth muscle hypertrophy, and angiogenesis.

In summary, asthma is an atopic/allergic disease that involves complex interactions among susceptible genes, immunological factors, infections, neuroendocrine factors, and environmental factors. Asthma is a common, chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.<sup>54</sup> This interaction can be highly variable among patients and within patients over time. This section presents a definition of asthma, a description of the processes on which that definition is based, the pathophysiology, pathogenesis, and natural history of asthma, with implications in the use of leukotriene receptor antagonist (LTRA) for treatment.

## Montelukast as a class of immunomodulant for asthma

Therapeutic management of asthma exacerbation and maintenance must take into account the complicated airway disease and its diverse pathophysiologic factors.<sup>52</sup> Since the 1980s, a new class of montelukasts has been available for the treatment of childhood asthma, and many clinical trials on montelukast have been published.

Montelukast (Singular<sup>®</sup>, Merck & Co., Inc., Whitehouse Station, NJ, USA) is a cysteinyl LTRA used for the maintenance treatment of asthma and to relieve symptoms of

seasonal allergies. Montelukast acts by blocking the action of leukotriene D4 (and secondary ligands, leukotrienes C4 and E4) on the cysteinyl leukotriene receptor CysLT1 in the lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene and results in less inflammation. Because of its method of operation, it is not useful for the treatment of acute asthmatic attacks.<sup>55</sup> The cysteinyl leukotrienes C4, D4, and E4 are end products of the arachidonic acid pathway and are potent mediators of antigen-induced contractions of airway smooth muscle.<sup>56</sup> Montelukast acts by antagonizing these compounds at their receptor, thus protecting against bronchoconstriction. It is the only LTRA currently licensed for use in children with asthma. The medication is available as chewable tablets, tablets, and sprinkle sachet formulation. It is taken once a day, preferably in the evening.

Another LTRA is zafirlukast (Accolate<sup>®</sup>, AstraZeneca plc, London, UK), taken twice daily. Zileuton (Zyflo<sup>®</sup>, Cornerstone Therapeutics Inc., Cary NC, USA), a drug used for the treatment of asthma, taken four times per day, blocks leukotriene synthesis by inhibiting 5-lipoxygenase, an enzyme of the eicosanoid synthesis pathway. It is mainly used as a complementary therapy in adults in addition to inhaled corticosteroids (ICSs) if they alone do not bring the desired effect.

There is well-accepted evidence that oral montelukast is an effective initial preventer therapy for children with mild asthma.<sup>57,58</sup> In addition, it seems to confer additional benefit as an add-on therapy to ICS in those who are inadequately controlled on ICS.<sup>59</sup> It is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchospasm. There is considerable interindividual heterogeneity in the efficacy of montelukast, but as yet, no firm clinical predictors of response have been identified.<sup>60</sup> Montelukast is generally safe and well tolerated; headache and gastrointestinal symptoms are the most commonly reported side effects.<sup>57</sup> Other side effects include hypersensitivity reactions, sleep disorders, drowsiness, increased bleeding tendency, hallucination, and possible mood changes and suicidal thoughts. Its use is associated with a higher incidence of Churg–Strauss syndrome (whether or not this drug is “unmasking” subclinical Churg–Strauss is as yet uncertain).

## **Effectiveness, clinical efficacy, and safety of montelukast in asthma: a literature review**

In this review, we performed an extensive literature search on the clinical efficacy and safety of montelukast. Research

reports were retrieved from PubMed and the Cochrane Database for Systematic Reviews for this review. Using the following search terms, we searched PubMed, Clinical Queries for articles: “asthma” AND “montelukast” AND “clinical efficacy”, “meta-analysis”, OR “safety”, OR “adverse effects”. We limited our search to include randomized trials, case control studies, and large case series. Limits were also set to include human studies and English language articles only, but with no time limits imposed. Studies were also found by reviewing the reference sections of the retrieved articles found in the Clinical Queries search. Studies on exercise-induced bronchospasm, viral-induced asthma, and smoking-induced asthma were separately searched and identified.

As of December 2013, we retrieved 48 articles from PubMed, Clinical Queries using the keywords “asthma” and “montelukast”. All randomized clinical trials (RCTs) and relevant case control studies were included. Review articles that did not provide any information on montelukast efficacy or side effects were excluded. Effectiveness relates to how well a treatment works in the practice of medicine, as opposed to efficacy, which measures how well treatment works in clinical trials or laboratory studies. Studies without evaluation of effectiveness/efficacy, safety, or adverse effects were not appraised in detail.

Among the 48 articles retrieved, only 25 were relevant articles, and 20 more articles (three meta-analyses and reviews and 17 RCTs, marked \* in Tables 1 and 2) were retrieved from the reference sections of the 25 articles as well as the authors’ own database and separate search. These are summarized as (systematic) reviews and meta-analyses in Table 1 and randomized trials in Table 2. There were 24 reviews and meta-analyses that involved pooling of data and statistical analyses. Relevant case control studies and cohorts are cited but not included in the tables.

Among the (systematic) reviews and meta-analyses, it is generally concluded that LTRAs should be considered when the combination of an ICS plus a long-acting beta 2-agonist (LABA) fails to satisfactorily control symptoms or after a failed trial of a LABA (Table 1).<sup>61,62</sup> These studies report that LTRA is generally inferior to ICS. One review shows that the risk of asthma exacerbations and hospitalizations is seven times higher in children on montelukast treatment than in those receiving ICSs.<sup>63</sup> However, LTRAs (montelukast, zafirlukast, and zileuton) may be used in patients with mild persistent asthma as well as in combination with other asthma medications at all levels of disease severity for long-term maintenance of asthma control.<sup>64</sup>

**Table 1** Systematic reviews and reviews of effectiveness and clinical efficacy of montelukast, with references listed in chronological order according to the year of publication

Population	Design	Efficacy and adverse effects	Remarks	References
Infants <24 months	Systematic review of RCTs and quasi-RCTs. 1,430 infants	Montelukast may reduce the frequency of postbronchiolitic wheezing without causing significant side effects, but that it has no effects on decreasing incidences of recurrent wheezing, symptom-free days, or the associated usage of corticosteroid in postbronchiolitis patients. Side effects of rash, vomiting, and insomnia caused by montelukast occurred in 1.5% of patients analyzed.	Small number of enrolled participants and inability to pool all clinical outcomes.	67*
Children and adults	Systematic review of RCTs	Improvements in symptoms and small-airways function after treatment with montelukast, whereas no relation existed with FEV1 improvement. Adverse effects not mentioned.	Improvements in clinical and laboratory parameters demonstrated.	54
1–18 years	RCTs: addition of antileukotriene (montelukast) to ICSs in mild to moderate asthma 17 RCTs	No evidence to support efficacy and safety of LTRAs as add-on therapy to low-dose ICS for children with uncontrolled asthma symptoms.	Low risk of bias, 5 trials of 559 children, conclusions valid. LTRA has no significant efficacy or adverse effects	83
Children and adults	Review article	In adults with asthma that is inadequately controlled on low doses of ICSs and showing significant reversibility with beta 2-agonists, LABA is superior to LTRA in reducing oral steroid treated exacerbations. Differences favoring LABA in lung function, functional status, and quality of life scores are generally modest. There is some evidence of increased risk of severe adverse effects with LABA. The findings support the use of a single inhaler for the delivery of LABA and ICSs. Unable to draw conclusions about which treatment is better as add-on therapy for children. ICSs are the treatment of first choice for the maintenance therapy of childhood asthma, irrespective of age or clinical phenotype, and the risk of asthma exacerbations and hospitalizations is seven times higher in children on montelukast treatment than in those receiving ICSs. Usefulness of primary care initiated or parent-led short courses of oral montelukast as adjunctive therapy for mild asthma exacerbations in children older than 2 years. No adverse effects. Inhaled fluticasone propionate/salmeterol were consistently greater compared to montelukast. No adverse effects. Schoolchildren and adolescents with mild to moderate persistent asthma. ICS had less asthma exacerbations, better lung function and asthma control than with montelukast. Insufficient data to determine whether the addition of montelukast to ICS improves outcome. No adverse effects. Pooled regression analysis. No relevant clinical or adverse effects	Good quality convincing trials are cited to support the conclusions.	63
Children	PubMed + Medline (1966–2006) search: double-blind randomized, placebo-controlled parallel-group study	Inhaled fluticasone propionate/salmeterol were consistently greater compared to montelukast. No adverse effects.	Five RCTs included. Level of evidence generally IB.	84
Children and adults	Retrospective analysis of four previously reported clinical trials	Schoolchildren and adolescents with mild to moderate persistent asthma. ICS had less asthma exacerbations, better lung function and asthma control than with montelukast. Insufficient data to determine whether the addition of montelukast to ICS improves outcome. No adverse effects.	Not a clinical trial in itself.	85
Children	Systematic review with meta-analysis of 18 relevant studies. Some already mentioned in this table	Usefulness of primary care initiated or parent-led short courses of oral montelukast as adjunctive therapy for mild asthma exacerbations in children older than 2 years. No adverse effects.	Well-performed meta-analysis to demonstrate ICS superior to montelukast.	86
15–45 years of age	Three randomized, double-blind, crossover trials evaluating single-dose montelukast 10 mg or placebo in patients (n=160) with EIB Comparative systematic review RCTs	Usefulness of primary care initiated or parent-led short courses of oral montelukast as adjunctive therapy for mild asthma exacerbations in children older than 2 years. No adverse effects.	Not a direct evaluation of effectiveness.	87*
Children	Review of eight studies	Compared with long-acting beta adrenoceptor agonists, LTRAs produce persistent attenuation of EIB and possess an additional effect with rescue short acting adrenoceptor agonists therapy in asthmatic patients with persistent EIB. A disadvantage of montelukast is a nonresponse phenomenon. ICSs are the first choice in pediatric persistent asthma. Montelukast monotherapy as an alternative treatment for the prevention of mild persistent pediatric asthma.	Sign criteria (evidence level and grades of recommendation) employed. No additional statistical analyses. Only few studies included.	65
Children	Review of eight studies	Compared with long-acting beta adrenoceptor agonists, LTRAs produce persistent attenuation of EIB and possess an additional effect with rescue short acting adrenoceptor agonists therapy in asthmatic patients with persistent EIB. A disadvantage of montelukast is a nonresponse phenomenon. ICSs are the first choice in pediatric persistent asthma. Montelukast monotherapy as an alternative treatment for the prevention of mild persistent pediatric asthma.	Sign criteria (evidence level and grades of recommendation) employed. No additional statistical analyses. Only few studies included.	88

Mean (SD) age 9.6 (2.1) years Adolescents and adults	Multivariate analysis  Systematic review of 13 studies	Long-term outcomes with ICS therapy better compared with treatment with leukotriene receptor antagonists. No adverse effects. Montelukast as add-on therapy to ICSs in the treatment of mild to moderate asthma improves control of asthma compared with ICS monotherapy. No significant adverse effects.	ICS is better, but montelukast still useful. Montelukast is useful as add-on therapy.	60  89
School-age children Children and adults	Meta-analyses of five randomized double-blind efficacy studies Review	ICS is the preferred first-line controller therapy for mild to moderate persistent childhood asthma to montelukast. Leukotriene receptor antagonists (montelukast and zafirlukast) are beneficial across a range of asthma severities and may have a particular role in exercise-induced asthma, aspirin-sensitive asthma, and individuals with concomitant allergic rhinitis. Hypersensitivity reactions, arthralgia, pulmonary eosinophilia, gastrointestinal disturbances, sleep disorders, respiratory infections, hallucinations, seizures, and raised liver enzyme levels are adverse effects. In asthmatic adults inadequately controlled on low doses of ICSs, the addition of LABA is superior to LTRA (montelukast or zafirlukast) for preventing exacerbations requiring systemic steroids, and for improving lung function, symptoms, and the use of rescue beta 2-agonists. No adverse effects.	Montelukast not as first-line controller. Unrestricted educational grant from AstraZeneca LP. Two LTRAs. Side effects listed.	90  68
Adults	Meta-analysis: eleven trials including 6,030 participants	Combination therapy with ICS and LABA was found to be more efficacious and cost effective compared with ICS alone or alternative combinations of controller medications. Montelukast is inferior. No adverse effects on montelukast. Use of ICS/montelukast compared with ICS/salbutamol resulted in similar odds of oral corticosteroid fills, decreased odds of emergency department visits and asthma related hospitalizations but higher utilization of short acting beta agonist. No adverse effects.	Montelukasts are inferior to LABA.	91
Children and adults	Systematic literature review of 11 clinical studies	Human pregnancy data for leukotriene modifiers (montelukast, zafirlukast, and zileuton) are limited to their reported use by nine pregnant women. No increased risk of preterm delivery caused by leukotriene modifiers was reported in these women. <sup>73</sup> Animal studies show no teratogenicity with montelukast or zafirlukast at doses much higher than the maximum recommended human daily doses. In contrast, zileuton has demonstrated adverse effects in fetal rats and a 2.5% incidence of cleft palate in rabbits at a dose equal to the maximum recommended human daily dose on a milligram per meters squared basis. The leukotriene modifiers (zafirlukast and montelukast) are rated pregnancy category B, based on safety in animal reproduction studies. Zileuton carries a pregnancy category C rating that is based on demonstrated risk in animal studies.	Evaluates combination therapy with ICS plus LABA than montelukast.	92
Children and adults	Retrospective analysis of matched cohort of 1,216 patients	In asthmatic adults inadequately controlled on low doses of ICSs, the addition of LABA is superior to LTRA (montelukast or zafirlukast) for preventing exacerbations requiring systemic steroids, and for improving lung function, symptoms, and the use of rescue beta 2-agonists. No adverse effects.	Large retrospective cohort. Some efficacy demonstrated.	93
Adults	Literature search on asthma controller therapy during pregnancy	Human pregnancy data for leukotriene modifiers (montelukast, zafirlukast, and zileuton) are limited to their reported use by nine pregnant women. No increased risk of preterm delivery caused by leukotriene modifiers was reported in these women. <sup>73</sup> Animal studies show no teratogenicity with montelukast or zafirlukast at doses much higher than the maximum recommended human daily doses. In contrast, zileuton has demonstrated adverse effects in fetal rats and a 2.5% incidence of cleft palate in rabbits at a dose equal to the maximum recommended human daily dose on a milligram per meters squared basis. The leukotriene modifiers (zafirlukast and montelukast) are rated pregnancy category B, based on safety in animal reproduction studies. Zileuton carries a pregnancy category C rating that is based on demonstrated risk in animal studies. In asthmatic adults inadequately controlled on low doses of ICSs, the addition of LABA is superior to LTRA for preventing exacerbations requiring systemic steroids and for improving lung function, symptoms, and use of rescue beta 2-agonists. LTRAs (montelukast, zafirlukast, and zileuton) may be used in patients with mild persistent asthma as well as in combination with other asthma medications at all levels of disease severity for long-term maintenance of asthma control. Leukotrienes should be considered as a therapeutic option or as additive therapy in patients with mild to severe asthma. No adverse effects.	Only nine pregnant women; no adverse effects on perinatal outcome.	95
Children and adults	12 RCTs	LTRA is superior to LTRA for preventing exacerbations requiring systemic steroids and for improving lung function, symptoms, and use of rescue beta 2-agonists. LTRAs (montelukast, zafirlukast, and zileuton) may be used in patients with mild persistent asthma as well as in combination with other asthma medications at all levels of disease severity for long-term maintenance of asthma control. Leukotrienes should be considered as a therapeutic option or as additive therapy in patients with mild to severe asthma. No adverse effects.	LTRA is inferior to LABA as add-on therapy.	96
Children and adults	Literature review	LTRA is superior to LTRA for preventing exacerbations requiring systemic steroids and for improving lung function, symptoms, and use of rescue beta 2-agonists. LTRAs (montelukast, zafirlukast, and zileuton) may be used in patients with mild persistent asthma as well as in combination with other asthma medications at all levels of disease severity for long-term maintenance of asthma control. Leukotrienes should be considered as a therapeutic option or as additive therapy in patients with mild to severe asthma. No adverse effects.	A review, not a study.	64
Children and adults	Review of controlled clinical studies in English	LTRA is superior to LTRA for preventing exacerbations requiring systemic steroids and for improving lung function, symptoms, and use of rescue beta 2-agonists. LTRAs (montelukast, zafirlukast, and zileuton) may be used in patients with mild persistent asthma as well as in combination with other asthma medications at all levels of disease severity for long-term maintenance of asthma control. Leukotrienes should be considered as a therapeutic option or as additive therapy in patients with mild to severe asthma. No adverse effects.	A review.	97

(Continued)

Table 1 (Continued)

Population	Design	Efficacy and adverse effects	Remarks	References
Primarily pregnant women	Review of controlled clinical studies in English	Safety issues: both zafirlukast and montelukast carry pregnancy category B classification whereas zileuton carries pregnancy category C classification. The most common adverse effects observed in clinical trials were headache, pharyngitis, abdominal pain, dyspepsia, and cough. Patients using chronic montelukast therapy experienced a statistically significant ( $P<0.05$ ) reduction in the use of short-acting beta agonists and antibiotics, suggesting improvement in asthma control. Chronic use of montelukast therapy is associated with a reduction of concomitant drug therapy costs.	Review. Provides some data on pregnancy adverse effects.	69
Adults	Retrospective cohort analysis of a primary care database in the UK (n=94)	Montelukast is indicated for the prophylaxis of chronic asthma in adults and children ( $\geq 6$ years). It may be considered as first-line therapy in patients with mild persistent asthma or for additional control in patients who are still symptomatic while receiving treatment with ICSs. It may also be used for additional control in aspirin-sensitive asthmatic patients. Consideration may be given for using montelukast to allow tapering of the dose of ICSs. Chronic treatment with montelukast can provide additional control of symptoms during exercise, but inhaled beta 2-agonists remain first-line therapy for prophylaxis and treatment.	Mainly cost analysis study.	98
Children and adults	MEDLINE search (up to May 1999) on relevant English language publications		Many newer studies not included.	66

Note: \*Additional references identified.

Abbreviations: EIB, exercise-induced bronchoconstriction; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta 2-agonist; LTRA, leukotriene receptor antagonist; RCT, randomized controlled trial; SD, standard deviation.

Exercise-induced bronchoconstriction (EIB) was specifically evaluated in two of the studies. In a comparative systematic review of RCTs in children, the authors conclude that compared with LABAs, LTRAs produce persistent attenuation of EIB and possess an additional effect with rescue short-acting adrenoceptor agonists therapy in asthmatic patients with persistent EIB.<sup>65</sup> Blake concludes that chronic treatment with montelukast can provide additional control of symptoms during exercise, but inhaled beta 2-agonists remain first-line therapy for prophylaxis and treatment.<sup>66</sup>

Postbronchiolitis wheezing is evaluated in a meta-analysis which concludes that montelukast may reduce the frequency of postbronchiolitic wheezing without causing significant side effects but that it has no effects on decreasing incidences of recurrent wheezing, symptom-free days, or the associated usage of corticosteroid in postbronchiolitis infants.<sup>67</sup>

Adverse effects of LTRAs are specifically commented on in two of the earlier studies. One review lists hypersensitivity reactions, arthralgia, pulmonary eosinophilia, gastrointestinal disturbances, sleep disorders, respiratory infections, hallucinations, seizures, and raised liver enzyme levels,<sup>68</sup> whereas the other lists headache, pharyngitis, abdominal pain, dyspepsia, and cough being the most common adverse effects observed in clinical trials.<sup>69</sup>

Among the RCTs, LTRAs are generally shown to be safe but inferior to ICS (Table 2). The majority of the randomized trials are placebo-controlled and montelukast as added-on trials. Most of these RCTs have relative small patient numbers. Nevertheless, one double-blind, multicenter, multinational study at 93 centers worldwide (n=689) demonstrates montelukast improves multiple clinical parameters of asthma control without important adverse effects.<sup>57</sup>

Three randomized control trials specifically evaluated EIB. In one RCT, children aged 6 to 18 years with EIB were randomized in a 4-week, placebo-controlled, double-blinded trial with montelukast or ICS (fluticasone propionate [FP]). The efficacy of montelukast for preventing a maximum decrease in forced expiratory volume in 1 second (FEV1) after exercise is significantly higher than that of FP, and the high leukotriene E4/fractional exhaled nitric oxide ratio is associated with a greater response to montelukast than to FP for EIB therapy.<sup>70</sup> Another randomized, double-blind, placebo-controlled, two-period crossover study evaluated the onset and duration of EIB attenuation in children after a single dose of montelukast and found single-dose montelukast provided rapid and sustained EIB attenuation in children.<sup>71</sup> Effect of montelukast was also shown to be better than salmeterol added to inhaled fluticasone on EIB in children

**Table 2** Randomized control trials of effectiveness and clinical efficacy of montelukast, with references listed in chronological order according to the year of publication

Population	Design	Efficacy and adverse effects	Remarks	References
16–49 years	Randomized, placebo-controlled trial, nonsmoking adults with postinfectious cough from 25 general practices in England. 276 patients to montelukast (n=137) or placebo (n=139); 70 (25%) patients had laboratory-confirmed pertussis	Montelukast is not an effective treatment for postinfectious cough in terms of quality of life and clinical parameters. Increased mucus production (montelukast, n=6; placebo, n=2), gastrointestinal disturbance (montelukast, n=3; placebo, n=5), and headache documented.	Multicenter trial documented no clinical efficacy.	74*
6–14 years	Randomized, double-blind, placebo-controlled, parallel study	No evidence that adding salmeterol or montelukast to ICSs can reduce the number of exacerbations in children with uncontrolled asthma. No significant adverse effects.	Clinical, laboratory, and quality of life assessments.	99
18–65 years	Randomized, comparative, multicenter clinical trial	Zileuton ER seems to be more efficacious than montelukast and well tolerated for the treatment of mild to moderate chronic persistent asthma in adult patient population. No adverse effects.	Another leukotriene.	100*
> 16 years, mean (SD) 52 (18.5) years	Randomized, double-blind, placebo-controlled trial in 100 patients	No benefit of addition of oral montelukast over conventional treatment in the management of acute asthma attack. No adverse effects.	No benefit in older children.	55*
6–18 years	Randomized, placebo-controlled, double-blinded trial with montelukast or ICS of 24 patients	FEV1 improvement only. No adverse effects mentioned.	Small study; only FEV1 assessed.	70*
Adults	Three parallel, 6-month, double-blind treatment arms: 347, 336, and 336 patients randomized to montelukast, fluticasone, and placebo, respectively.	In a population of asthmatic patients actively smoking cigarettes, both 10 mg/day montelukast and 250 µg of fluticasone propionate twice daily significantly increased the mean percentage of days with asthma control compared with placebo. No difference between montelukast and ICS in terms of effectiveness or side effects.	Only evaluated asthma control in days. An alternative treatment for smokers.	75*
Adults	Randomized placebo control of 87 patients	Additional administration of oral montelukast results in a significantly higher PEF the morning after admission than that achievable with current standard treatment in acute asthma. No adverse effects.	Not-intention to treat. Only peak flow improvement demonstrated.	101*
4–14 years	Randomized, double-blind, placebo-controlled, two-period crossover study (n=66)	FEV1 assessment. Single-dose montelukast provided rapid and sustained EIB attenuation in children. No adverse effects mentioned.	Small study; only FEV1 assessed.	71*
5–18 years	Randomized, double-blind, parallel-group, 12-month pilot trial	ICS a better choice as initial asthma therapy than montelukast in children with newly diagnosed asthma. No adverse effects.	In 60 children montelukast generally inferior.	102
Children 5–12 years	Double-blind, randomized placebo controlled trial on 117 children	Single-dose oral montelukast added to standard therapy of inhaled bronchodilators and systemic glucocorticoids did not provide additional clinical benefit in children with acute moderate to severe asthma. No adverse effects.	In-patients with moderate to severe asthma attacks only.	103*
6–14 years	Randomized, double-blind, double-dummy, multicenter, two-period, 4-week, crossover study; 154 patients randomized, 145 completed	Attenuation and response of EIB to albuterol rescue after exercise challenge were significantly better with montelukast than with salmeterol after 4 weeks of treatment. No adverse effects.	FEV1 response only. Not intention-to-treat.	72*
Adults	Randomized double-blind trial of 20 asthmatic subjects with documented hyperpnea-induced bronchoconstriction	FEV1 and urinary biomarkers. No significant effects. Fish oil supplementation should be considered as an alternative treatment for EIB. Montelukast useful but not superior.	Effects on FEV1 and urinary biomarkers.	73*
6–14 years	Randomized, double-blind, placebo-controlled study	Interim analysis 27 patients. Moderate acute asthma exacerbations, oral montelukast (5 mg) added to standard therapy is unlikely to result in additional FEV1 improvements in 3 hours.	Small sample size interim study with no efficacy.	104*

(Continued)

Table 2 (Continued)

Population	Design	Efficacy and adverse effects	Remarks	References
2–14 years	Double-blind, randomized, placebo-controlled trial on 194 asthmatic children	Montelukast added to usual treatment reduced the risk of worsened asthma symptoms and unscheduled physician visits during the predictable annual September asthma epidemic.	Some clinical efficacy demonstrated.	105*
Adults	Multicenter, placebo-controlled, double-blind, double-dummy, crossover trial. 44 nonsmokers and 39 light smokers with mild asthma were assigned randomly to treatment twice daily with inhaled beclomethasone and once daily with oral montelukast	Primary outcome was change in prebronchodilator FEV1 in smokers versus nonsmokers. Secondary outcomes included peak flow, PC(20) methacholine, symptoms, quality of life, and markers of airway inflammation. Beclomethasone significantly reduced sputum eosinophils and eosinophil cationic protein in both smokers and nonsmokers but increased FEV1 (170 mL, $P=0.0003$ ) only in nonsmokers. Montelukast significantly increased morning peak flow in smokers (12.6 L/min, $P=0.002$ ) but not in nonsmokers.	Small sample sizes but clinical efficacy demonstrated.	76*
Children and adults	Systematic literature review of eleven clinical studies	Combination therapy with ICS and LABA was found to be more efficacious and cost effective compared with ICS alone or alternative combinations of controller medications. Montelukast is inferior. No adverse effects on montelukast.	Evaluates combination therapy with ICS plus LABA.	92
2–5 years	Randomized, double-blind, placebo-controlled, parallel-group of 51 patients	A single 4 mg tablet of montelukast provided additive clinical benefit in mild to moderate acute asthma in preschool-aged children when administered concomitantly with short-acting beta 2-agonist bronchodilators as the initial treatment. No adverse effects.	Small study. Demonstrate efficacy in mild to moderate disease in preschool children.	106*
6–24 months	Randomized, double-blind, placebo-controlled, parallel-group	In 256 patients, no demonstrable efficacy or adverse effects between montelukast and placebo.	Not 1:1 randomization or intention-to-treat. Large sample size.	58*
2–5 years	Double-blind, multicenter, multinational study at 93 centers worldwide (n=689).	Montelukast improves multiple clinical parameters of asthma control, without important adverse effects.	Large multicenter study. Efficacy of montelukast demonstrated.	57*
Mean (SD) age 10.4 (2.2) years	Multicenter, randomized, double-blind, crossover study (n=279)	Improved asthma control significantly, indicated by a small additive effect on lung function and a clinically relevant decrease in asthma exacerbation days. No adverse effects.	Added on efficacy demonstrated clinically.	59*

**Note:** \*Additional references identified.

**Abbreviations:** EIB, exercise-induced bronchoconstriction; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta 2-agonist; PC(20), concentration to produce a 20% fall in FEV1 from baseline; PEF, peak expiratory flow; SD, standard deviation.



in a randomized, double-blind, double-dummy, multicenter, two-period, 4-week, crossover study.<sup>72</sup> Also, both fish oil and montelukast have been shown to reduce the severity of EIB, but montelukast is not superior to fish oil.<sup>73</sup>

A randomized, placebo-controlled trial on nonsmoking adults from 25 general practices in England showed montelukast was not an effective treatment for postinfectious cough.<sup>74</sup> Nevertheless, smoking is a relevant issue in asthma, especially in adult patients. Price et al evaluated 10 mg/day montelukast and 250 µg of fluticasone propionate twice daily, each compared with placebo, in patients with self-reported active smoking and asthma. Both 10 mg/day montelukast and 250 µg of fluticasone propionate twice daily significantly increased the mean percentage of days with asthma control compared with placebo.<sup>75</sup> In another multicenter, placebo-controlled, double-blind, double-dummy, crossover trial, 44 nonsmokers and 39 light smokers with mild asthma were assigned randomly to treatment twice daily with inhaled beclomethasone and once daily with oral montelukast. In subjects with mild asthma who smoke, the response to ICSs was attenuated, suggesting that adjustments to standard therapy may be required to attain asthma control. The study demonstrated greater improvement in some outcomes in smokers treated with montelukast.<sup>76</sup>

These systematic reviews and RCTs published between 1999 and 2013 led to the conclusions in most asthma management guidelines that ICS should remain the first-line therapy for persistent asthma in children. LTRAs (primarily montelukast) are not the first choice for persistent severe asthma.<sup>3</sup> LTRAs should be considered when the combination of an ICS plus a LABA fails to satisfactorily control symptoms or after a failed trial of a long-acting beta 2-agonist. However, several studies suggest that when evaluating outcome parameters other than lung function (in particular exacerbation frequency), LTRAs may have efficacy similar to LABAs. Indeed, many patients using ICSs have relatively normal FEV1, suggesting that underlying inflammation and airway hyperresponsiveness are the driving forces behind continued episodic airflow obstruction and symptoms. The FEV1 response was also documented in a cohort of 22 atopic asthmatic children aged 7 to 16 years with reproducible EIB. A once daily treatment with oral montelukast attenuated the immediate-phase response (FEV1) and abolished the late-phase response induced by means of exercise challenge in asthmatic children.<sup>77</sup> Disuse of add-on LTRAs (odds ratio: 1.42; 95% confidence interval: 1.06–1.74) was independently associated with moderate to severe symptoms in adult patients with recurrent exacerbations of asthma,

especially in association with recurrent episodes of upper respiratory tract infections (URI).<sup>78</sup> In these patients, add-on therapy with a LTRA would appear to be a reasonable therapeutic option in an attempt to more completely attenuate airway hyperresponsiveness and suppress inflammation. Since the long-term safety of LABAs and their associated risks of increased asthma exacerbations have been highlighted, add-on therapy with a LTRA might even become the preferred therapeutic approach.<sup>61,62</sup> Patients themselves may also express a desire to avoid LABAs since the US Food and Drug Administration has advised that labeling be produced to outline the “small but significant risk in asthma related deaths” associated with their regular use. Furthermore, it could be argued that patients with persistent asthma and concomitant allergic rhinitis using ICSs alone should preferentially be given an LTRA instead of a LABA. On the other hand, the use of high doses of ICSs in very young children may lead to adverse effects such as adrenal suppression and reduced growth velocity. Nevertheless, in a real-world clinical setting subjects were more adherent to ICS + LABA therapy than ICS + LTRA therapy. ICS + LABA therapy seems to be more effective than ICS + LTRA therapy in the management of asthma, regardless of adherence.<sup>79</sup> URIs represent the most frequent cause of acute asthma exacerbations. Use of an LTRA for adult asthmatic patients appears to reduce the incidences of URIs alone and acute asthma exacerbations without URI, but it failed to prevent URI-induced acute asthma exacerbations once a URI occurred, unless combined with ICS.<sup>80,81</sup>

The LTRAs generally have low adverse effect profiles, which include hypersensitivity reactions, arthralgia, pulmonary eosinophilia, gastrointestinal disturbances, sleep disorders, respiratory infections, hallucinations, seizures, raised liver enzyme levels, headache, pharyngitis, abdominal pain, dyspepsia, and cough.<sup>68,69</sup> In particular, a significant increase in alkaline phosphatase level may occur in some children following LTRA.<sup>68,82</sup> Agitation symptoms may also occur that subside after drug withdrawal.<sup>82</sup>

In conclusion, LTRAs can be used as a monotherapy or as an add-on therapy in addition to ICS. They may be an effective alternative in asthma control and safe even with long-term usage. The advantages of LTRAs include low risks of side effects and rapid onset of action and achievement of peak effect. The fact that medication has to be given orally only once a day and that no inhaler is necessary will help to improve patient satisfaction and compliance, especially in the pediatric age group. Montelukast has a place in the treatment of young children with viral-triggered wheezing diseases,

exercise-induced asthma, and in children whose parents are steroid-phobic and find ICS unacceptable. The judicious use of montelukast may lead to a reduction in health care visits, a savings in health care dollars, better asthma control, and reduced amount of time off school and from work.

## Disclosure

The authors report no conflicts of interest in this work.

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