

Montelukast in the treatment of asthma and allergic rhinitis

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Practice Points

- Montelukast is used in the treatment of both asthma and allergic rhinitis.
- Montelukast is included in asthma guidelines as an adjunctive anti-inflammatory therapy.
- Montelukast should not be used as first-line treatment for allergic rhinitis.
- Montelukast is well tolerated and side effects are generally mild.

SUMMARY Asthma and allergic rhinitis are common diseases that impact a large number of people worldwide. Safe and effective treatments are needed to reduce the morbidity and, in asthma, the mortality associated with them. In this article, we review the use of a leukotriene receptor antagonist, montelukast, in the treatment of these conditions. This article provides an overview of the pharmacology of montelukast and the guideline recommendations for its use in asthma and allergic rhinitis.

Leukotriene: basic pharmacology & approved indications

Leukotrienes are lipid mediators produced by inflammatory cells such as mast cells and basophils during the early phase, and eosinophils and macrophages during the late phase [1]. The cysteineinyl leukotrienes include leukotriene C₄, D₄ and E₄. They play a role in the pathogenesis of allergic inflammation in the upper and lower airways. They are derived from arachidonic acid via the 5-lipoxygenase pathway. Their role in the pathogenesis of asthma derives from their effects on smooth muscle tone, mucous secretion, microvascular permeability and chemotactic effects. They also promote dendritic cell maturation, which in turn promotes the generation of further allergic stimulation. The levels

of cysteinyl leukotrienes have been shown to be elevated in patients with symptomatic allergic rhinitis (AR) [2]. Montelukast is a selective leukotriene receptor antagonist that inhibits the cysteinyl leukotriene receptor 1. Cystinyl leukotriene receptor 1 is found on inflammatory cells, smooth muscle cells and endothelium in the respiratory mucosa of both the upper and the lower airway.

Montelukast is used in the treatment of both asthma and AR. It is indicated for the prophylaxis and chronic treatment of asthma in patients 2 years and older [3]. In adults, montelukast can be used to treat asthma if the patient remains symptomatic after intermittent short-acting β-agonists and cannot or will not use an inhaled corticosteroid (ICS). It is also indicated for the

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relief of symptoms of seasonal AR in patients 15 years and older when other treatments are not effective or tolerated.

Montelukast is administered as a tablet of 10 mg in adults 15 years or older, 5 mg in children aged 6–14 years, 4 mg in children aged 2–5 years. It is available as quick-dissolve granules for administration to young children. The pharmacokinetic profile allows for it to be administered once a day.

What is asthma?

Asthma may be considered as a chronic inflammatory disease of the airways in which the airflow obstruction returns to, or towards, normal with anti-inflammatory treatment [4]. To avoid the side effects of oral administration, ICS are accepted as the gold standard of anti-inflammatory treatment. When patients remain uncontrolled despite adherence to ICS, we suggest switching to foundation therapy with a combination inhaler, including the addition of a long-acting β -agonist (LABA) to the ICS in a single ICS/LABA inhaler [4,5,10]. Guidelines promote applying this concept in a stepwise approach to gain current control and reduce future risk of exacerbations.

In asthma most patients remain uncontrolled

It is easy for both physicians and patients to be complacent with day-to-day asthma management. Surveys in Canada consistently show that more than half of asthma patients remain uncontrolled and this has not changed significantly over the last decade [6].

One recent study of 350 primary care physician in Canada confirmed that 60% of nearly 11,000 current patients were uncontrolled by one or more parameters of the Canadian Asthma Control Questionnaire (ACQ) at routine office visits [6]. This was shown to be associated with the patients being six-times more likely to have an unscheduled physician visit, 3.5-times more likely to end up in the emergency room and twice as likely to be admitted to hospital with asthma compared with an asthmatic who was currently controlled [6].

Although there is mounting interest in adopting new models of chronic disease management for asthma, outside of specialist practice it is unusual for asthmatics to be regularly followed specifically for their asthma or AR. Although

they are seen more often, asthma is not assessed nor management addressed in these visits unless they are presenting with an asthma worsening or exacerbation.

Most physicians adhere to national or international guidelines with respect to management of many chronic diseases, however, guidelines are based on efficacy of randomized controlled trials (RCTs), which may not reflect day-to-day practice [7]. Patients may often have concerns about long-term therapy and prefer the symptomatic relief offered by antihistamines in AR and short-acting β -agonists in asthma. Patients may also have significant concerns or misperceptions about potential side effects from commonly prescribed medications (i.e., ICS). A plethora of different ICS dosage regimens and devices compound these concerns.

Montelukast being a simple, once-daily NSAID with efficacy in both AR and asthma may explain the effectiveness of oral antileukotrienes in office management of asthma and AR.

Asthma & asthma with AR

■ Clinical evidence: summary of recent clinical data & postmarketing data Adding montelukast or salmeterol to ICS: a RCT

To assess the effect of montelukast versus salmeterol when added to the ICS, fluticasone propionate, on asthma exacerbation in patients whose symptoms are inadequately controlled with fluticasone alone, a 52-week, two-period, double-blind, randomized controlled multicenter trial, during which patients whose symptoms remained uncontrolled by ICS were randomized to add montelukast or salmeterol, was conducted. 1490 asthma patients were randomized. The primary end point was the percentage of patients with at least one asthma exacerbation during the 1-year follow-up. A total of 20.1% of the patients in the group receiving montelukast and fluticasone had an asthma exacerbation, compared with 19.1% in the group receiving salmeterol and fluticasone [8].

Montelukast in a real-life asthma study

Two parallel, multicenter, pragmatic trials to evaluate the real-world effectiveness of a leukotriene-receptor antagonist (LTRA) as compared with either an ICS for first-line asthma-controller therapy or a LABA as add-on therapy in patients already receiving ICS therapy.

Eligible primary care patients were between 12 and 80 years of age and had impaired asthma-related quality of life (Mini Asthma Quality of Life Questionnaire score ≤ 6) or inadequate asthma control (ACQ score ≥ 1). They randomly assigned patients to 2 years of open-label therapy, under the care of their usual physician, with a LTRA (148 patients) or an ICS (158 patients) in the first-line controller therapy trial and a LTRA (170 patients) or a LABA (182 patients) added to an ICS in the add-on therapy trial. Study results at 2 months suggest that the LTRA was equivalent to an ICS as first-line controller therapy and to LABA as add-on therapy for diverse primary care patients. Equivalence was not proved at 2 years [9].

RADAR trial: montelukast in asthma & AR

To evaluate the effectiveness of montelukast as add-on therapy for patients diagnosed with asthma and concurrent AR that remain uncontrolled while on ICS monotherapy or ICS/LABA with any product and at any dosage in a 'real-world' setting. An 8 week, multicenter, open-label, observational study was conducted. Patients were ≥ 15 years old, and, while treated with an ICS or ICS/LABA had AR and uncontrolled asthma symptoms by at least two criteria as per the Canadian Asthma Consensus Guidelines. The primary outcome measure was the percentage of patients with controlled asthma symptoms after 8 weeks of treatment with montelukast 10 mg once a day added to ICS or ICS/LABA therapy.

A total of 319 patients were enrolled in the 8-week assessment. At baseline, all patients had uncontrolled asthma symptoms based on the Canadian Asthma Consensus Guidelines; at the 8-week assessment, 229 (76.1%) patients achieved asthma control. According to the ACQ (ACQ score ≤ 0.75), 164 (54.7%) achieved well-controlled asthma at week 8. The mean ACQ score decreased from 2.03 (SD: 0.80) to 0.92 (SD: 0.80; $p < 0.001$) for all patients, representing a clinically significant improvement. A statistically and clinically significant reduction in the overall Mini Rhinoconjunctivitis Quality of Life Questionnaire score was also achieved with a mean decrease of -1.45 (SD: 1.35) from 2.57 (SD: 1.20) to 1.12 (SD: 1.00; $p < 0.001$). Patient and physician satisfaction with montelukast add-on therapy were also significantly increased when compared with baseline treatment [10].

Place in therapy

Asthma guideline recommendations

Montelukast is a widely prescribed LTRA, orally administered anti-inflammatory therapy for asthma. It is included in the Global Initiative for Asthma guidelines as an adjunctive anti-inflammatory therapy for all severities of asthma requiring anti-inflammatory treatment in addition to other therapy, instead of or as well as ICS or ICS/LABA combination inhalers [4,5,10].

The relative cost of anti-inflammatory therapy in persistent asthma has been assessed. It has been determined that using a combination of fluticasone-salmeterol is more cost effective than using montelukast alone as initial maintenance therapy for persistent asthma in patients treated with a short-acting β_2 -agonist only [11]. For children with mild-to-moderate persistent asthma, low-dose fluticasone had lower cost and higher effectiveness compared with montelukast [12].

AR

Clinical evidence: summary of recent clinical data & postmarketing data

AR is an allergen-induced, upper-airway inflammatory disease characterized by hyperactive airway mucosa resulting in symptoms of rhinorrhea, sneezing, nasal pruritus, and congestion, with associated symptoms of red, itchy, watery eyes, itching of the palate and throat, and cough. AR is widely recognized as being the most common allergic disorder, but detailed estimates of its actual prevalence are lacking. Canadian prevalence studies suggest the life-time prevalence of AR to be between 39 and 52% [13]. AR has a significant economic burden as it is common in young working adults and can cause poor sleep, interruption of daily activities and can increase the severity of associated asthma.

When compared with placebo, montelukast improves disease-specific quality of life of patients with persistent AR [14].

A 32-week randomized, placebo-controlled crossover study in patients with persistent AR but no associated respiratory disease, compared antihistamine treatment alone or in combination with montelukast. The results showed that montelukast alone or in combination with an antihistamine gave a gradual increase in nasal symptom improvement within 6 weeks of treatment in patients with persistent AR [15]. Similar results have been shown in patients with seasonal AR [16].

Nitric oxide (NO) is a mediator with the potential to cause inflammation, and NO imbalance appears to be important in the pathogenesis of AR. NO is synthesized from L-arginine by NO synthase. Arginase competes with NO synthase for arginine. Therefore, increased serum arginase activity could potentially limit NO production. Montelukast reduced serum arginase levels in patients with seasonal AR and this may be a novel mechanism of action of montelukast that is worthy of further study [17].

Corticosteroids have wide-ranging anti-inflammatory and immunosuppressive effects and often are seen as the 'gold standard' comparator in trials of novel therapies for allergic disease. Compared to montelukast, fluticasone propionate has been shown to significantly improve daytime and nighttime seasonal AR symptoms [18]. It has been shown that adding montelukast to nasal steroid therapy does not improve nasal symptom scores in patients with seasonal AR [19] or perennial AR [20]. However, montelukast is administered systemically and has the potential to have effects remote from the nose. Compared with topical nasal steroids and topical antihistamine, montelukast had the greatest effect on ocular itching and throat and palate itching [21]. However this effect was not seen in asthmatics administered montelukast in a placebo-controlled trial, although the need for inhaled β_2 -agonists was significantly lower during montelukast treatment [22]. An environmental challenge chamber study in ragweed-sensitized patients has shown that antihistamines have a more rapid onset of action than montelukast [23]. Montelukast alone improves perennial AR symptoms when compared with placebo [24].

Health economics is becoming an increasingly important consideration. AR is one of the top ten reasons for a primary care visit (a review of insurance data in the USA has shown that newly diagnosed AR patients who are given montelukast as first-line therapy have higher medical costs and resource utilization in the year following treatment initiation than those prescribed first-line branded second-generation antihistamines [fexofenadine, desloratidine and cetirizine]) [25,26]. This finding was not related to demographics, available disease severity or comorbidity confounders. Asthmatic subjects were specifically excluded from the analysis. Some of the effect may be related to the higher medication cost of montelukast, but patients prescribed

montelukast were more likely to need additional AR medications and other medical services. It can be inferred from this study that montelukast is inferior to second-generation antihistamines as first-line therapy for AR [26].

A systematic review and meta-analysis of the use of montelukast in AR has shown that montelukast reduces nasal symptom scores when compared with placebo. Montelukast is not as effective as topical nasal steroids or antihistamines and should be regarded as second-line therapy. If montelukast is used in the treatment of AR it should be in combination with an antihistamine [27].

Montelukast has also been compared with subcutaneous immunotherapy (SCIT). It has been shown that SCIT is more effective than montelukast in the treatment of seasonal AR [28] in patients with birch pollen-induced moderate asthma and rhinitis, the addition of SCIT provides a greater clinical benefit than that of montelukast [29].

Increased levels of leukotrienes have been found in the nasal secretions of patients with viral infections of the upper airways [30]. Therefore, it was hypothesized that treatment with montelukast may reduce the incidence of respiratory tract infection. A randomized control trial of montelukast for 12 weeks in children aged 1–5 years without a history of reactive airways disease failed to show any benefit in preventing the development of upper respiratory tract infections [31]. This result is not surprising, as the increased levels of leukotrienes are likely to be secondary to the presence of the virus, rather than indicating a susceptibility to infection.

Montelukast has a role to play in maintenance treatment of AR; however, its effects are not as great as those of antihistamines and substantially less than topical corticosteroids. Montelukast should be considered a second-line treatment and should be used in combination with an antihistamine.

■ Place in therapy Allergy guideline recommendations

The Allergic Rhinitis and its Impact on Asthma guidelines 2010 have recommendations for the use of montelukast in the treatment of rhinitis with or without asthma [32]. In patients without asthma, oral leukotriene receptor antagonists are recommended in adults and children with seasonal AR and in preschool children with

perennial AR. In adults with perennial allergic rhinitis oral leukotriene receptor antagonists are not recommended. In patients with AR and asthma, inhaled glucocorticosteroids, are recommended over oral leukotriene receptor antagonists as a single controlling medication for asthma. In patients with AR and asthma who prefer not to use or cannot use inhaled glucocorticosteroids or in children whose parents do not agree to use inhaled glucocorticosteroids, oral leukotriene receptor antagonists for the treatment of asthma are recommended.

Patient selection

In patients with AR it can be a useful addition to therapy in those sensitized to both seasonal and perennial allergens. It should not be used as monotherapy, and should not be considered as a first-line therapy. It has a particular usefulness in patients who have upper airways disease, in particular nasal polyps, with coexistent asthma. It also has a particular role in patients with aspirin-sensitive disease.

Dosage & administration in both asthma & AR

The recommended dose in adults 15 years and older is 10 mg to be taken once daily in the evening. The dose for pediatric patients 6–14 years is a 5 mg chewable tablet to be taken in the evening, or one packet of 4 mg granules to be taken in the evening. No dose adjustment is needed in the elderly or those with renal insufficiency. Additionally, no dose modification is needed in mild-to-moderate liver failure; its use has not been studied in severe liver failure. The only absolute contraindication to the use of montelukast is hypersensitivity to the drug or any ingredient in the formulation. The patient should be educated about the preventive nature of montelukast, and advised to take it even when their asthma is well-controlled, they should also be advised that it should not be used to treat acute attacks. Montelukast has not been studied in pregnant and lactating women and that it should only be used if clearly needed.

Tolerability & adverse events

In general, montelukast is well tolerated, side effects are mild and generally do not require discontinuation of the drug. In a study specifically looking at safety and adverse effects, there was generally no clinical or laboratory differences

in adverse reactions versus placebo. Side-effects commonly reported included headache, otitis media, upper respiratory tract infection and pharyngitis [33].

A review of eight studies has shown that adverse events occurred at a similar frequency in patients taking either montelukast or placebo [34].

Postmarketing surveillance systems, usually assessing side effects, are not as fully developed as our knowledge and understanding of RCTs to prove drug efficacy. Neuropsychiatric adverse events, including agitation, aggressive behavior, depression and insomnia have been reported in association with LTRAs. There have been concerns about an association between montelukast and suicidality, and in 2008 the US FDA stated that it was investigating this suspected association further [102]. Following the FDA announcement there was a sevenfold increase in the number of montelukast-related cases reported to the Adverse Event Reporting System database in the USA [103]. There have also been sporadic reports of the introduction of montelukast being associated with the development of Churg–Strauss syndrome, but this has usually been associated with the reduction of systemic corticosteroids that may have led to worsening of the underlying vasculitis rather than montelukast being a direct cause of the condition.

Conclusion

Table 1 summarizes the current evidence for the use of montelukast in the treatment of asthma and AR.

There have been two relevant Cochrane reviews [35,36]. A review of the evidence for the use of leukotriene receptor antagonists for nonspecific cough in children concluded that there was not enough evidence to support its use [35]. In adults with asthma that is inadequately controlled on low doses of inhaled steroids and showing significant reversibility with β_2 -agonists, LABAs are superior to leukotriene receptor antagonists in reducing oral steroid-treated exacerbations [36].

Oral therapy with an antileukotriene, Montelukast, has widespread application for the real-life, day-to-day, anti-inflammatory management of asthma and AR. We have identified some of the current literature on montelukast, which, in conjunction with national and international guidelines in both asthma and AR, should help assist healthcare professionals perhaps re-examine the role of montelukast in their asthma and allergy practice.

Table 1. Important studies of montelukast in the treatment of asthma and allergic rhinitis.

Study (year)	Comparison	Conclusion	Ref.
Asthma			
Bjerner <i>et al.</i> (2003)	Montelukast and fluticasone compared with salmeterol and fluticasone	The addition of montelukast when symptoms are uncontrolled could provide equivalent control to salmeterol	[8]
Price <i>et al.</i> (2011)	Comparison of montelukast and inhaled steroid and addition of either montelukast or LABA as add-on therapy	At 2 months montelukast was equivalent to inhaled steroid as first-line therapy and to LABA as add-on. Equivalence was not proved at 2 years	[9]
Keith <i>et al.</i> (2009)	Open-label observational study of patients with uncontrolled asthma	Montelukast is effective for managing asthma and allergic rhinitis symptoms in patients who were previously uncontrolled with ICS or ICS/LABA	[10]
Allergic rhinitis			
Ciebiada <i>et al.</i> (2008)	Montelukast with or without antihistamine	Combining montelukast with an antihistamine significantly improved quality of life compared with each agent alone	[37]
Patel <i>et al.</i> (2005)	Montelukast versus placebo	Montelukast significantly reduced perennial allergic rhinitis symptoms during 6 weeks of treatment	[24]
Martin <i>et al.</i> (2006)	Fluticasone versus montelukast	Fluticasone significantly reduced daytime and night-time seasonal allergic rhinitis symptoms	[18]

ICS: Inhaled corticosteroid; LABA: Long-acting β -agonist.

Ongoing properly designed effectiveness and postmarketing surveillance trials are sorely needed in primary care, including both objective efficacy outcomes, and incorporating patient-reported outcomes. The information should be integrated into practice guidelines to not only improve patient symptoms, but to assist in improving outcomes by gaining and maintaining control and reducing future risk of exacerbations. It is possible that montelukast may reduce regrowth of nasal polyps following surgery; this is an area that requires further study. There also needs to be more research into the effectiveness of using montelukast to treat preschool wheeze.

Financial & competing interests disclosure

H Neighbour has participated in CME presentations organized by Merck and GlaxoSmithKline. A McIvor has received honoraria for providing medical education and attending advisory meetings for pharmaceutical companies involved in the management of asthma including: AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKlein, Merck, Novartis and Takeda. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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