

Montelukast for prevention and treatment of asthma exacerbations in adults: Systematic review and meta-analysis

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ABSTRACT

It has proven efficacy in reducing asthma exacerbations, but the effect size of montelukast (a leukotriene receptor antagonist) for varied severity of asthma exacerbations is not systematically assessed. This study was designed to systematically explore the evidence for montelukast, as first-line or add-on therapy, in preventing and treating asthma exacerbations in adult patients with asthma. Randomized controlled trials were searched in PubMed, CENTRAL, Web of Science, Embase, and OVID up to March 2013, where montelukast prevented or treated asthma exacerbations in adults. Primary outcomes were the number of patients experiencing exacerbations in chronic asthma and hospitalizations in acute asthma. Odds ratio (OR) with 95% confidence intervals (CI), risk difference, and number needed to treat (NNT) were calculated and pooled. Adverse events were also assessed in chronic asthma. Twenty trials for chronic asthma and six for acute asthma were identified. In comparison with placebo, adults with chronic asthma receiving montelukast had significantly reduced number of exacerbations (OR = 0.60 and 95% CI, 0.49, 0.74; NNT = 17 and 95% CI, 12, 29). However, montelukast was inferior to inhaled corticosteroids (ICSs) (OR = 1.63; 95% CI, 1.29, 2.0) and ICS plus long-acting beta₂-agonist (LABA; OR = 3.94; 95% CI, 1.64, 9.48) as the first-line therapies and LABA (OR = 1.22; 95% CI, 1.05, 1.42) as the add-on therapies in reducing asthma exacerbations. In acute asthma, montelukast could statistically improve peak expiratory flow percent predicted ($p = 0.008$) and reduce systemic corticosteroid intake ($p = 0.005$). Montelukast had low risk in hoarseness and insomnia. Our meta-analysis suggests that montelukast significantly reduces mild, moderate, and part of severe exacerbations in chronic mild to moderate asthma, but it has inferior efficacy to ICS or ICS plus LABA.

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Asthma is a chronic respiratory disease, affecting up to 10% of adults in the Western World.¹ Most adults (83.1%) had either “not well” or “very poorly” controlled asthma in a nationwide random sample in the United States.² Despite advances in knowledge of the pathophysiology of asthma and the availability of effective therapy, asthma can not be cured currently.

The purpose of asthma management is to achieve a total asthma control that involves current control and future risk.³ Asthma exacerbations, as the most important future risk, are common in the lives of asthmatic patients. Prevention of asthma exacerbations has been identified in all asthma treatment guidelines as an important component of establishing ideal asthma control.⁴ Thus, it is relevant to consider different strategies for maintaining control and to identify those that are most effective in reducing asthma exacerbations.

Asthma exacerbations vary in severity from mild transient events to severe life-threatening ones. A recently published American Thoracic Society/European Respiratory Society (ATS/ERS) statement defines severe asthma exacerbations as events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma, moderate exacerbations as events that result in a temporary change in treatment, in an effort to prevent the exacerbation from becoming severe, and mild exacerbations that are just outside the normal range of variation in symptoms or changes in flow rates for the individual patient and may reflect transient loss of asthma control.⁴ Inhaled corticosteroids (ICSs) and combination of ICS/long-acting β_2 -agonists (LABA) are the mainstay therapy for reducing asthma exacerbations including severe ones,^{5,6} but

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some patients require additional treatment or prefer not use ICS. Leukotriene receptor antagonists (LTRAs) are effective in the treatment of persistent asthma, exercise-induced asthma, and aspirin-induced asthma; some patients respond to LTRA better than ICS, so a personalized approach to asthma pharmacotherapy is recommended.⁷

Although montelukast in licensed dose, as a potent and specific CysLT1 receptor antagonist, is inferior to ICS in reducing asthma exacerbations,³ it has proven better efficacy in the control of asthma exacerbations than placebo.⁸ Therefore, the effect size of montelukast for varied severity of asthma exacerbations remains unclear. Furthermore, evidence of montelukast for treating acute asthma exacerbations is being established. In this systematic review and meta-analysis, we weighed the relative effect size of montelukast for preventing asthma exacerbations under different standard treatment conditions and determined whether montelukast is effective in the treatment of acute asthma in adults.

METHODS

Search Strategy and Selection Criteria

We searched electronic databases including PubMed (1966 to March 2013), CENTRAL (Cochrane Controlled Trials Register; issue 1, 2013), Web of Science (1994 to March 2013), Embase (up to March 2013), and OVID (up to March 2013) for randomized controlled trials (RCTs) using a comprehensive search strategy including the following keywords: “asthma exacerbation” or “acute asthma” and montelukast or “leukotrienes receptor antagonist.” We reviewed reference lists of all included studies, systematic reviews, and narrative reviews to identify potentially relevant citations. There was no limitation on language or publication year.

We included trials if they met the following criteria: trials with chronic asthma were RCTs comparing montelukast versus placebo or other active drugs (ICS, ICS/LABA, theophylline, *etc.*), and trials reporting at least one asthma exacerbation in the results section of studies or in the adverse events of using montelukast. We excluded one crossover trial because this study had inadequate follow-up, poor ascertainment of exacerbation data, and time-treatment interactions that were difficult to evaluate.⁹ The trials in which the patients were being hospitalized for acute asthma were excluded because the prespecified primary outcome in these studies was the number of patients experiencing hospitalization for acute asthma. After exclusion of duplicates, H.P.Z. and C.E.J. reviewed the full text of all citations with titles and abstracts that seemed to fit the criteria of inclusion. Citations that were clearly not relevant or were not RCTs, were not reviewed in full.

The numbers of citations rejected and the reasons for rejection were tracked.

Data Extraction and Quality Assessment

We reviewed each identified citation, and we obtained the full text of all definite or possible RCTs, irrespective of language. Trials were assessed independently by two reviewers (H.P.Z. and C.E.J.) and from each article we extracted details of authors, year of publication, sex, sample size, asthma severity, standard treatments, interventions as the first-line or add-on therapies, outcomes, adverse events, and so on. The two reviewers independently assessed risk of bias to determine methodological quality using the Cochrane Collaboration’s tool for systematic reviews of interventions.¹⁰ If information was not reported adequately, we requested details from the authors. Any disagreement between reviewers was resolved by consensus.

Primary and Second Outcomes

In chronic asthma, the number of asthma exacerbations was specified as primary outcomes, and the number of detailed different exacerbations such as unscheduled visits, requiring systemic corticosteroids, emergency room visits and hospitalizations were identified as second outcomes. For acute asthma, hospitalizations for acute asthma were regarded as primary outcomes, and other outcomes such as use of systemic corticosteroids and treatment failure were identified as second outcomes.

Statistical Analysis and Assessment and Evaluation of the Evidence Quality

The included trials were divided into two types of analyses according to the stages of asthma (chronic asthma and acute asthma). Then, the trials were further stratified by montelukast as the first-line or the add-on therapies. The mean daily dose of ICSs in asthma subjects was converted to micrograms of beclomethasone equivalent.³ We treated asthma exacerbations as dichotomous variables expressed with odds ratio (OR) and the weighted mean difference was reported for lung function test (forced expiratory volume in 1 second [FEV₁] or peak expiratory flow) as continuous outcomes considering the weight of each study.

Heterogeneity was assessed by means of the Cochran Q method and by the test of inconsistency (I^2). A random effects model was used if the Q statistic ($p < 0.1$) or I^2 ($>50\%$) was significant, or we used a fixed effects model. We performed subgroup analysis to assess the source of heterogeneity and assessed the presence of publication bias visually with a funnel plot. All results were reported with 95% confidence intervals (CIs) and all p values were two-tailed. The analysis was per-

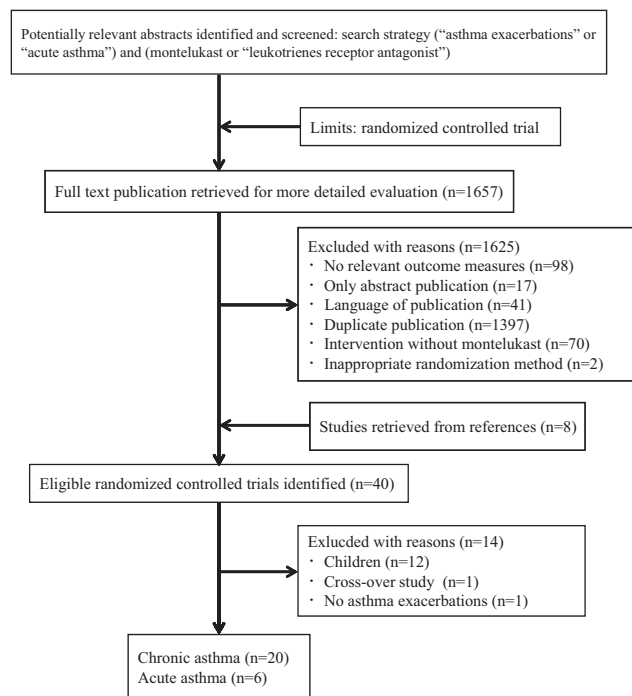


Figure 1. Flow diagram of trial selection and details of study identification, inclusion, and exclusion.

formed using RevMan 5 program (The Cochrane Collaboration, Oxford, U.K.) and Stata Version 11.0 (Stata Corp. LP, College Station, TX).

The quality of the evidence related to the estimation of benefits and disadvantages in the adult population followed the suggestions of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group¹¹ by adopting the use of GradePro software 3.2.2.¹²

RESULTS

Trials Include Study Characteristics and Quality of Reporting

Figure 1 shows details of study identification, inclusion, and exclusion. Our search strategy initially yielded 1657 citations. Of these, we included 20 trials for chronic asthma^{13–32} and six for acute asthma^{33–38} in adults. The characteristics of each study are listed in Tables E1 and E2 (online supplement). In studies with chronic asthma, median treatment duration was 12 weeks and in all studies with acute asthma, the licensed dosage of montelukast was administered only once. FEV₁% predicted at baseline in chronic asthma was >40%. In general, rescue β_2 -agonists were permitted.

Most of the included studies were of high methodological quality (Table 1). Double blinding was used in five trials in acute asthma except for one using the single-blind design and in 18 of 20 trials in chronic asthma except for two using the open-label design.

Primary Outcomes in Chronic Asthma

Asthma Exacerbations. Compared with those having placebo, adults with chronic asthma receiving montelukast therapy had a significantly reduced number of exacerbations (OR = 0.60 and 95% CI, 0.49, 0.74; number needed to treat [NNT] = 17 and 95% CI, 12, 29; heterogeneity not significant, I^2 = 25.6% and p = 0.224). Further subgroup analyses indicated that montelukast could decrease asthma exacerbations either in the first-line (OR = 0.54 and 95% CI, 0.39, 0.74; NNT = 13 and 95% CI, 8, 29) or the add-on regimens (OR = 0.58 and 95% CI, 0.34, 0.97; NNT = 30 and 95% CI, 16, 306) in comparison with placebo. However, montelukast treatment was inferior to ICS (OR = 1.63; 95% CI 1.29, 2.0) and ICS plus LABA (OR = 3.94; 95% CI, 1.64, 9.48) as the first-line therapies and LABA (OR = 1.22; 95% CI, 0.05, 1.42) as the add-on therapies.

We analyzed the relative effect size of montelukast for preventing asthma exacerbations compared with some active treatments. Among these active treatments as the first-line regimens, ICS plus LABA is the most effective one, but there is no statistical difference between montelukast and LABA as the first-line therapy, both of which are significantly inferior to ICS (Fig. 2). In addition, we considered actual treatments including the standard antiasthma medications in these trials (Fig. 3). ICS, montelukast plus ICS, and twofold ICS were comparable, but all are inferior to ICS plus LABA. It only reached the statistical trend that ICS plus LABA was superior to montelukast plus LABA (OR = 2.32; 95% CI, 0.91, 5.94; p = 0.079).

Our subgroup and sensitivity analysis in placebo-controlled studies indicated that asthma patients with concomitant allergic rhinitis would get much more benefit from montelukast in comparison with those without allergic rhinitis (OR = 0.55 and 95% CI, 0.43, 0.70, versus OR = 0.74 and 95% CI, 0.52, 1.03), especially in the add-on therapy (OR = 0.54 and 95% CI, 0.31, 0.94, versus OR = 0.96 and 95% CI, 0.96, 4.79). The therapy duration of either <12 or >12 weeks did not change the benefit of reduced asthma exacerbations from montelukast (OR = 0.35 and 95% CI, 0.20, 0.61, versus OR = 0.65 and 95% CI, 0.53, 0.81). In our analysis, we did not find any difference for montelukast in reducing asthma exacerbations compared with placebo in the trials supported by the company (OR = 0.59; 95% CI, 0.47, 0.74) and those without any support of company (OR = 0.65; 95% CI, 0.43, 0.99).

Second Outcomes in Chronic Asthma

The second outcomes such as systemic corticosteroid intake, emergency room visits, unscheduled visits, and hospitalizations were reported in adults with chronic asthma. Montelukast as the first-line therapy was superior to placebo in patients requiring systemic corti-

Table 1 Methodological quality of included studies in chronic and acute asthma

Study	Allocation Sequence Adequately Generated	Allocation Adequately Concealed	Multicenter	Blinding	Complete Outcome Data Adequately Addressed	Free of selective Outcomes Reporting	Other Bias	Intention to Treat	Sample Size Calculation	Power	Conflict of Interest
Chronic asthma											
Reiss <i>et al.</i> 1998 ¹³	Yes	Yes	Yes	Double blind	Yes	Yes	Unclear	Yes	Yes	0.95	No
Noonan <i>et al.</i> 1998 ¹⁴	Yes	Yes	Yes	Double blind	Yes	Yes	Unclear	Yes	Yes	0.80	No
Malmstrom <i>et al.</i> 1999 ¹⁵	Yes	Yes	Yes	Double blind	Yes	Yes	No	Yes	Yes	0.95	No
Laviolette <i>et al.</i> 1999 ¹⁶	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	No	Yes	0.95	No
Nelson <i>et al.</i> 2000 ¹⁷	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.80	No
Busse <i>et al.</i> 2001 ¹⁸	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.80	Yes
Fish <i>et al.</i> 2001 ¹⁹	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	No	Yes	0.80	No
Calhoun <i>et al.</i> 2001 ²⁰	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	No	NA	Yes
Israel <i>et al.</i> 2002 ²¹	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	No	Yes	0.80	No
Meltzer <i>et al.</i> 2002 ²²	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.80	Yes
Pearlman <i>et al.</i> 2002 ²³	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.80	No
Vaquero <i>et al.</i> 2003 ²⁴	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.90	No
Ringdal <i>et al.</i> 2003 ²⁵	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.90	NA
Grosclaude <i>et al.</i> 2003 ²⁶	Yes	No	Yes	No	Yes	Unclear	Unclear	Yes	No	NA	Yes
Bjerner <i>et al.</i> 2003 ²⁷	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.80	Yes
Price <i>et al.</i> 2003 ²⁸	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.90	Yes
Illowite <i>et al.</i> 2004 ²⁹	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.80	NA
Wise <i>et al.</i> 2007 ³⁰	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.80	Yes
Deykin <i>et al.</i> 2007 ³¹	Yes	Yes	Yes	Double blind	Yes	Unclear	Unclear	Yes	Yes	0.90	Yes
Price <i>et al.</i> 2011 ³²	Yes	No	Yes	No	Yes	No	No	Yes	Yes	0.90	Yes
Acute asthma											
Ferreira <i>et al.</i> 2001 ³³	Yes	Yes	No	Double blind	Yes	Yes	No	No	No	NA	No
Camargo <i>et al.</i> 2003 ³⁴	Yes	Yes	Yes	Double blind	Yes	Yes	No	Yes	Yes	0.80	No
Cýllý <i>et al.</i> 2003 ³⁵	Yes	Unclear	No	Single blind	Yes	Yes	Unclear	No	No	NA	No
Camargo <i>et al.</i> 2010 ³⁶	Yes	Yes	Yes	Double blind	Yes	No	No	Yes	Yes	0.97	Yes
Ramsay <i>et al.</i> 2011 ³⁷	Yes	Yes	No	Double blind	Yes	Yes	No	No	Yes	0.80	Yes
Adhchi <i>et al.</i> 2012 ³⁸	Yes	Yes	Yes	Double blind	Yes	Yes	Unclear	No	Yes	0.85	Yes

NA = not available.

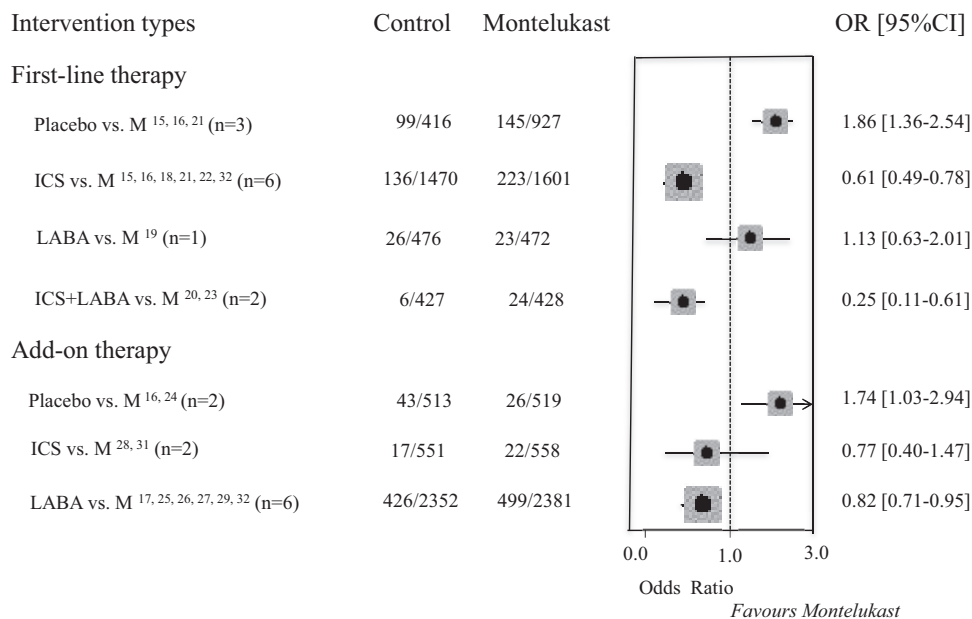


Figure 2. Pooled OR of patients experiencing exacerbations, comparing controlled drugs with montelukast. Trials stratified according to controlled drugs and intervention types. OR, odds ratio.

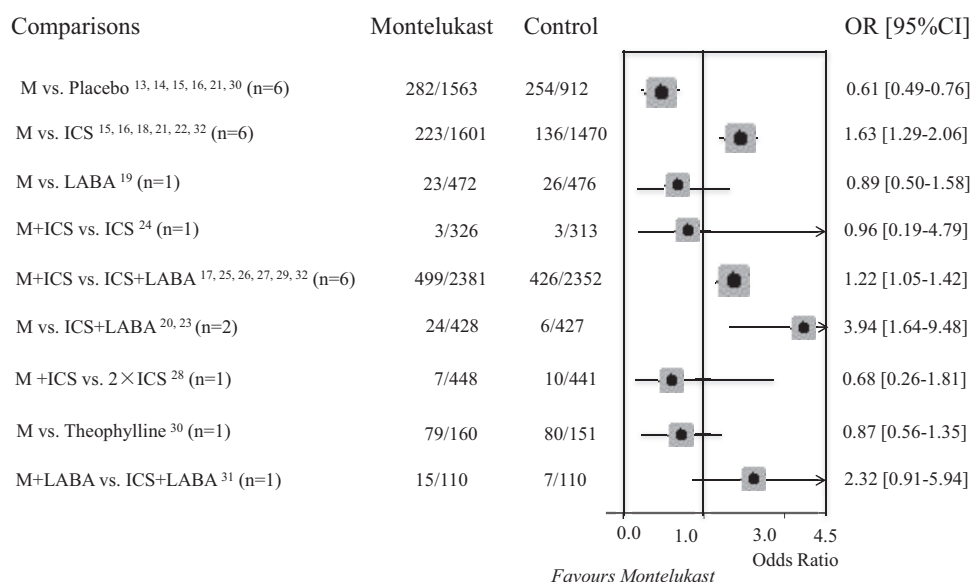


Figure 3. Pooled OR of patients experiencing exacerbations in actual treatments including the standard antiasthma medications in these trials, comparing montelukast with controlled drugs. OR, odds ratio.

costeroids (OR = 0.35; 95% CI, 0.13, 0.93), but in the mixed add-on and first-line therapies, we found that there was not a statistically significant difference in requiring systemic corticosteroids (OR = 0.79; 95% CI, 0.54, 1.17) and emergency room visits (OR = 0.74; 95% CI, 0.44, 1.25) between montelukast and placebo. Furthermore, in the first-line therapy, no statistical difference was indicated in requiring systemic corticosteroids (OR = 0.73; 95% CI, 0.30, 1.75) and unscheduled visits (OR = 2.32; 95% CI, 0.91, 5.94) between montelukast and ICS. In addition, montelukast as the add-on therapy was inferior to LABA in unscheduled visits (OR = 1.29; 95% CI, 1.03, 1.61) but not in requiring systemic corticosteroid (OR = 1.06; 95% CI, 0.87, 1.29), emergency room visits (OR = 0.99; 95% CI, 0.63, 1.56), and hospitalization (OR = 0.66; 95% CI, 0.27, 1.61).

Primary and Second Outcomes in Acute Asthma

In adults with acute asthma, there was a trend for montelukast reducing hospitalizations (OR = 0.72; 95% CI, 0.50, 1.06; $p = 0.09$) when compared with placebo. Montelukast could statistically improve peak expiratory flow percent predicted ($p = 0.008$) and reduce systemic corticosteroid intake (OR = 0.43; 95% CI, 0.23, 0.81; $p = 0.005$), but it did not reduce treatment failure (OR = 0.80; 95% CI, 0.58, 1.12; $p = 0.314$) for acute asthma.

Safety

Adverse events in chronic asthma are listed in Table 2. The incidence of adverse events (excluding asthma exacerbations) between montelukast and placebo or

Table 2 Adverse events in montelukast, placebo, and active drugs in adults with chronic asthma

Adverse Events	No. of Studies	Incidence (%) in Montelukast Group	No. of Patients with Events (montelukast vs control)	OR (95% CI)
Montelukast vs placebo in adults with chronic asthma				
Headache ^{13,14,15,16,24}	5	16.79 (14.86, 18.86)	233/1388 vs 142/818	1.05 (0.83, 1.33)
Bronchitis ^{16,24}	2	2.28 (1.18, 3.94)	12/527 vs 7/361	0.79 (0.31, 2.05)
Influenza ^{15,16,24}	3	8.53 (6.80, 10.53)	78/914 vs 47/618	1.25 (0.84, 1.84)
Nausea ^{16,30}	2	6.39 (5.83, 10.52)	29/454 vs 23/302	1.06 (0.66, 1.78)
Pharyngitis ^{13,14,15,16,24}	5	4.73 (3.68, 5.98)	66/1394 vs 50/960	0.82 (0.56, 1.20)
Rash ¹⁶	1	2.4 (0.94, 4.73)	7/201 vs 3/148	0.52 (0.13, 2.17)
Sinusitis ^{13,15}	2	7.06 (5.16, 9.39)	43/609 vs 24/321	1.00 (0.59, 1.69)
Upper respiratory tract infection ^{13,15,16,24}	4	20.12 (17.99, 22.39)	266/1322 vs 164/891	0.90 (0.71, 1.14)
Montelukast vs active drugs in adults with chronic asthma				
Headache ^{15,16,18,19,20,22,23,25,29}	9	5.23 (4.45, 6.07)	162/3096 vs 137/2969	1.01 (0.79, 1.29)
Bronchitis ^{16,25}	2	2.98 (1.75, 4.73)	17/570 vs 8/556	2.11 (0.90, 4.94)
Influenza ^{15,16,25}	3	5.22 (3.90, 6.83)	50/957 vs 37/708	0.86 (0.56, 1.34)
Nausea ^{16,23,30}	3	7.11 (5.14, 9.52)	41/577 vs 29/567	1.41 (0.85, 2.32)
Pharyngitis ^{15,16}	2	6.29 (4.47, 8.57)	37/588 vs 32/451	0.89 (0.54, 1.45)
Rash ^{16,18}	2	1.73 (0.75, 3.38)	8/463 vs 5/471	1.62 (0.53, 5.01)
Sore throat ^{18,22,25}	3	1.01 (0.46, 1.90)	9/895 vs 18/885	0.49 (0.22, 1.10)
Upper respiratory tract infection ^{15,16,25}	3	13.48 (11.38, 15.81)	129/957 vs 123/807	0.88 (0.66, 1.17)
Abnormal ALT ^{15,29}	2	4.78 (3.61, 6.19)	54/1130 vs 29/981	1.24 (0.77, 2.00)
Hoarseness ^{18,20,22,29}	4	0.54 (0.23, 1.05)	8/1481 vs 20/1470	0.37 (0.20, 0.90)
Insomnia ^{19,22}	2	0.00 (0.00, 0.50)	0/736 vs 8/734	0.11 (0.01, 0.87)
Oral pharyngeal candidiasis ^{18,22,25}	3	0.11 (0.00, 0.62)	1/895 vs 14/885	0.13 (0.03, 0.57)

OR = odds ratio; CI = confidence intervals; ALT = alanine aminotransferase.

active therapies in adults with chronic asthma were similar or presented no significant differences except for hoarseness (OR = 0.43; 95% CI, 0.20, 0.90, insomnia (OR = 0.11; 95% CI, 0.01, 0.87) and oral pharyngeal candidiasis (OR = 0.13; 95% CI, 0.03, 0.57). Furthermore, we found one asthma-related death in the salmeterol group.²⁷ In trials of acute asthma, the adverse events were not pooled because of the small number of studies, but the incidence of adverse events was similar or not significantly different between montelukast and placebo in most of trials.

Assessment and Recommendation of Montelukast for Chronic and Acute Asthma in Adults

The evidence of the benefits of montelukast in reducing asthma exacerbations and treating acute asthma in adults can be extrapolated by using GRADE (Table 3). In adults with chronic asthma, the evidence of montelukast as add-on therapy compared with placebo, first-line/add-on therapy compared with ICS, and add-on therapy compared with LABA was of moderate or high quality. Furthermore, in acute asthma, the evidence of

montelukast in reducing hospitalizations, systemic corticosteroid intake and treatment failure compared with placebo was of moderate quality.

DISCUSSION

Asthma exacerbations are common events in the lives of asthmatic patients. Despite what is detailed in the National Asthma Education and Prevention Program guidance, asthma management and control in U.S. patients is unsatisfactory.³⁹ In adults with chronic mild-to-moderate asthma, montelukast significantly reduced asthma exacerbations either in the first-line or the add-on regimens, but it was inferior to ICS or ICS plus LABA with fewer adverse events. Asthmatic patients with concomitant allergic rhinitis benefit much more from montelukast than those without. Furthermore, montelukast could improve lung function and reduce systemic corticosteroid intake in acute asthma. Although montelukast is very expensive, especially in developing countries, many asthma patients are still willing to take it as their conventional medication to get better asthma control. It is suggested that the com-

Table 3 The quality of evidence assessment for montelukast in prevention and treatment of asthma by GRADE approach

Clinical outcomes	Comparisons	Population	Therapy Types	Illustrative Comparative Risk		Relative Effect (95% CI)	No. of Participants (studies)	Quality of Evidence (GRADE)
				With Comparator	With Intervention			
Chronic asthma								
Asthma exacerbations	Montelukast vs placebo ^{15,16,20}	Adults	First line	238/1000	144/1000 (109 to 188)	OR = 0.574 (0.39, 0.74)	1343 (n = 3)	Moderate 1
Asthma exacerbations	Montelukast vs placebo ^{16,24}	Adults	Add-on	84/1000	50/1000 (30 to 82)	OR = 0.58 (0.34, 0.97)	1032 (n = 2)	Moderate 2
Asthma exacerbations	Montelukast vs ICS ^{15,16,18,21,22,32}	Adults	First line	93/1000	142/1000 (116 to 174)	OR = 1.63 (1.29, 2.06)	3071 (n = 6)	Moderate 3
Asthma exacerbations	Montelukast vs ICS ^{28,31}	Adults	Add-on	31/1000	40/1000 (21 to 74)	OR = 1.31 (0.68, 2.5)	1109 (n = 2)	High 4
Asthma exacerbations	Montelukast vs LABA ^{17,25,26,27,29,31}	Adults	Add-on	181/1000	213/1000 (188 to 239)	OR = 1.22 (1.05, 1.42)	4733 (n = 6)	High 5
Asthma exacerbations	Montelukast vs ICS plus LABA ^{20,23}	Adults	First line	14/1000	53/1000 (23 to 119)	OR = 3.94 (1.64, 9.48)	855 (n = 2)	Moderate 6
Acute asthma								
PEF% predicted	Montelukast vs placebo ^{33,37}	Adults	NA		10.65	MD = 10.65 (2.81, 18.49)	93 (n = 2)	Very low 7
Hospitalization	Montelukast vs placebo ^{34,36,38}	Adults	NA	169/1000	128/1000 (93 to 178)	OR = 0.72(0.50, 1.06)	925 (n = 3)	Moderate 8
The number of patients requiring oral steroids	Montelukast vs placebo ^{33,34}	Adults	NA	711/1000	648/1000 (603 to 693)	OR = 0.75 (0.62, 0.92)	221 (n = 2)	Moderate 9
Incidence of treatment failure	Montelukast vs placebo ^{34,36}	Adults	NA	277/1000	246/1000 (204 to 295)	OR = 0.85 (0.67, 1.09)	772 (n = 2)	Moderate 10
1 (–1 Limitations) Three trials (Malmstrom 1999, Laviolette 1999 and Israel 2002) all have high quality, but Laviolette 1999 and Israel 2002 fail to adhere to an intention-to-treat analysis, suggesting high likelihood of bias (–1 of quality).								
2 (–1 Limitations) Laviolette 1999 fail to adhere to an intention-to-treat analysis, suggesting high likelihood of bias (–1 of quality).								
3 (–1 Inconsistency; +1 imprecision; +1 plausible confounding would reduce a demonstrated effect.) Substantial heterogeneity across trials with the five trials showing OR >1, but one trial (Israel 2002) showing OR = 0.746. Lower limit of 95% CI is very close to 1.0 and it is uncertain if lower limit would be below 1.0 with additional trials. Some plausible confounding factors (e.g., smoking status, body mass index, and different asthma phenotypes would reduce a demonstrated effect.								
4 (–1 Imprecision; +1 plausible confounding would reduce a demonstrated effect.) Wide 95% CI that precludes any conclusion about the effects of montelukast on asthma exacerbation in adult patients. Some plausible confounding factors (e.g., smoking status and body mass index) and different asthma phenotypes would reduce a demonstrated effect.								
5 (–1 Inconsistency; +1 large effect.) Substantial heterogeneity across trials with the five trials showing OR > 1, but one trial (Price 2011) showing OR = 0.910. The effect is large in the absence of other methodological limitations (the no. of participants = 4733).								
6 (–1 Imprecision; –1 publication bias; +1 large effect.) Wide 95% CI (1.638, 9.478) that precludes any conclusion about the effects of montelukast on exacerbation in adult patients with asthma. Only two trials were included, from the funnel plot we strongly suspected there was publication bias. Large effect (M-H pooled OR = 3.940) in the absence of other methodological limitations, so upgrading quality of evidence.								
7 (–1 Limitations; –1 imprecision.) Two of the trials fail to adhere to an intention-to-treat analysis, suggesting high likelihood of bias (–1 of quality). Wide 95% CI that precludes any conclusion about the effects of montelukast on PEF% predicted in adult patients with acute asthma.								
8 (–1 Imprecision.) Wide 95% CI that precludes any conclusion about the effects of montelukast on hospitalization in adult patients with acute asthma.								
9 (–1 Risk of bias). One trial (Ferreira 2001) of the two trials fail to adhere to an intention-to-treat analysis, suggesting high likelihood of bias (–1 of quality).								
10 (–1 Imprecision). Wide 95% CI that precludes any conclusion about the effects of montelukast on incidence of treatment failure in adult patients with acute asthma. PEF = peak expiratory flow; OR = odds ratio; CI = confidence intervals; ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonists. NA = not available; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation.								

1 (–1 Limitations) Three trials (Malmstrom 1999, Laviolette 1999 and Israel 2002) all have high quality, but Laviolette 1999 and Israel 2002 fail to adhere to an intention-to-treat analysis, suggesting high likelihood of bias (–1 of quality).

2 (–1 Limitations) Laviolette 1999 fail to adhere to an intention-to-treat analysis, suggesting high likelihood of bias (–1 of quality).

3 (–1 Inconsistency; –1 imprecision; +1 plausible confounding would reduce a demonstrated effect.) Substantial heterogeneity across trials with the five trials showing OR > 1, but one trial (Israel 2002) showing OR = 0.746. Lower limit of 95% CI is very close to 1.0 and it is uncertain if lower limit would be below 1.0 with additional trials. Some plausible confounding factors (e.g., smoking status, body mass index, and different asthma phenotypes would reduce a demonstrated effect.

4 (–1 Imprecision; +1 plausible confounding would reduce a demonstrated effect.) Wide 95% CI that precludes any conclusion about the effects of montelukast on asthma exacerbation in adult patients. Some plausible confounding factors (e.g., smoking status and body mass index) and different asthma phenotypes would reduce a demonstrated effect.

5 (–1 Inconsistency; +1 large effect.) Substantial heterogeneity across trials with the five trials showing OR > 1, but one trial (Price 2011) showing OR = 0.910. The effect is large in the absence of other methodological limitations (the no. of participants = 4733).

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7 (–1 Limitations; –1 imprecision.) Two of the trials fail to adhere to an intention-to-treat analysis, suggesting high likelihood of bias (–1 of quality). Wide 95% CI that precludes any conclusion about the effects of montelukast on PEF% predicted in adult patients with acute asthma.

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10 (–1 Imprecision). Wide 95% CI that precludes any conclusion about the effects of montelukast on incidence of treatment failure in adult patients with acute asthma. PEF = peak expiratory flow; OR = odds ratio; CI = confidence intervals; LABA = long-acting β_2 -agonists. NA = not available; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation.

bination of a cumulative dose for leukotriene D₄ and leukotriene D₄/methacholine potency ratio might be useful to identify leukotriene-responsive asthmatic patients.⁴⁰ As a review reported, montelukast could replace ICS as first-line medications for asthmatic patients who are refractory to ICS or can not use inhalant devices.⁴¹

Although prevention of asthma exacerbations has been identified in all asthma treatment guidelines, only in the past 10 years have exacerbations been used as a primary outcome variable in asthma. According to the recently published ATS/ERS statement, definitions of a mild or moderate asthma exacerbation are not justifiable.⁴ In 7 of 20 trials,^{14,17,19,24,27,29,30} the primary outcome was asthma exacerbation, but in the rest of studies, asthma exacerbations were described in the adverse events or safety section of montelukast. Montelukast as the first-line therapy was significantly inferior to low-dose ICS from 352 to 400 µg daily, but there was statistically significant difference in reducing systemic corticosteroid intake (OR = 0.73; 95% CI, 0.30, 1.75; *p* = 0.477) and unscheduled visits (OR = 2.32; 95% CI, 0.91, 5.94; *p* = 0.079) was not found between montelukast and ICS. Interestingly, we did not find any difference in reducing asthma exacerbations between montelukast and LABA as the first-line therapy (OR = 0.89; 95% CI, 0.50, 1.58; *p* = 0.68), but it showed statistical significance in the add-on therapies (OR = 1.22; 95% CI, 1.05, 1.42; *p* = 0.01), which could result from the interaction of ICS and LABA. The mechanism may relate to the benefits of the anti-inflammatory effects of ICS, together with the LABA as a bronchodilator and a functional antagonist (protecting against bronchoconstrictor stimuli), and the synergism of the combination on airway eosinophilic inflammation.

According to the Global Initiative for Asthma, physicians can choose low-dose ICS or LTRAs as the controller option in step 2, but they should know the difference in reducing asthma exacerbations between them from our study. Furthermore, there are three controller options for step 3, which are low-dose ICS plus LABA, medium- or high-dose ICS/low-dose ICS plus LTRAs, and low-dose ICS plus theophylline. Our study indicated that ICS plus LABA was superior to montelukast plus ICS that was less effective than medium- or high-dose ICS. One study in a real-world clinical setting, considering adherence of subjects to ICS plus LABA therapy seems to be more effective than ICS plus montelukast therapy.⁴² Traditionally, asthma has been considered a disease that predominantly involves the large airways, but this concept is being challenged now and increasing evidence has shown that small airway dysfunction is present in mild asthma.⁴³ Furthermore, a higher degree of small airways dysfunction is associated with more frequent asthma exacerbations. Therefore, asthmatic patients

with normal FEV₁ values and poor disease control and small airway function should be investigated.⁴⁴ It is difficult for coarse particle but not extrafine particle ICS to reach the small airways defined as airways with an internal diameter of <2 mm, referring to the landmark study of Macklem and Mead.⁴⁵ A review also showed that the effect of greater asthma control may be explained by increased delivery to the small airways by the extrafine formulation.⁴⁶ Receptors for leukotrienes are expressed at higher levels in fibroblasts derived from the small airways than the large airways, possibly resulting in a predominant effect of montelukast on the small airways.⁴⁷

LTRAs are well established in the management of chronic asthma, but there is little information in acute asthma. Our study was different from Watts and colleagues.⁴⁸ First, we only focused on montelukast but no other LTRAs such as zafirlukast in acute asthma. Second, there were two more trials^{37,38} in adults included in our study. Third, in our study the effect of montelukast on requiring systemic corticosteroid was also observed. As a result, we found statistically reduced systemic corticosteroid intake when added to usual care. We must point out that in all included trials montelukast was administrated only once in acute asthma. It is suggested that the course for montelukast in treating acute asthma has not been established.

There are some strengths in our study. First, we conducted an unprecedented meta-analysis to systematically explore the effects of montelukast on different asthma exacerbations. Second, the varied objective outcomes for measuring asthma exacerbations were used according to the ATS/ERS statement.⁴ Third, we analyzed the absolute and relative effects of montelukast on asthma exacerbations and achieved its effect size in the first-line or different add-on therapies evaluated by GRADE approach, which could be translated into clinical practice. Fourth, we performed some subgroup and sensitivity analyses including the multitudinous first-line/add-on therapies, allergic rhinitis, treatment course, and company support in chronic asthma, which were not performed in other studies.^{8,49–51}

Our study also has some limitations. First, although high-quality RCTs were included, the primary outcome was just asthma exacerbation in only 7 of 20 trials, which could lower the power. Second, as we know, smoking, obesity, adherence, and age are factors modifying the response to antiasthma medications, but this information was not available in most included studies. Third, although most publications may have been produced with montelukast, there are still significant articles reporting on effects of other compounds (zafirlukast, pranlukast, zileuton, *etc.*) that modify the leukotriene pathway. However, we did not pool these studies because great heterogeneity existed in the previous study.⁸

CONCLUSIONS

In conclusion, our study suggests that montelukast significantly reduces mild, moderate, and part of severe asthma exacerbations either in the first-line or the add-on regimens and prefer patients with concomitant allergic rhinitis to others, but it is inferior to ICS or ICS plus LABA with few adverse events. Furthermore, one dose of montelukast could improve lung function and reduce systemic corticosteroid intake in acute asthma.

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