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Leukotriene receptor antagonists versus placebo in the treatment of asthma in adults and adolescents: a systematic review and meta-analysis

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Abstract

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Background—Leukotriene receptor antagonists (LTRAs) are recommended as alternative treatment in patients with mild asthma, but their effect compared with placebo is unclear.

Purpose—To determine the benefits and harms of LTRAs as monotherapy or in combination with inhaled corticosteroids compared with placebo in adults and adolescents with asthma.

Data sources—MEDLINE and the Cochrane Central Register of Controlled Trials from inception through June 2015.

Study selection—Peer-reviewed, English-language, randomized controlled trials in patients with asthma that reported the effect of LTRAs versus placebo on measures of asthma control.

Data extraction—Three researchers extracted data on the study population, interventions, outcome measures, adverse events, and study methodology were extracted in duplicate.

Data synthesis—Of 2008 abstracts screened, 50 trials met eligibility criteria. Random-effects meta-analyses and meta-regression were performed. In six trials of LTRA monotherapy, LTRAs reduced the risk of an exacerbation (summary risk ratio [RR] = 0.60, 95% CI 0.44, 0.81). In four trials of LTRA as an add-on to inhaled corticosteroids, the summary RR for exacerbation was 0.80 (95% CI: 0.60, 1.07). LTRAs significantly increased FEV₁ either as monotherapy or as add-on to inhaled corticosteroids, whereas FEV₁ % predicted was only improved in trials of LTRA monotherapy. Adverse event rates were similar in the intervention and comparator groups.

Limitations—Variation in definitions and reporting of outcomes, high risk of bias, heterogeneity, and possible selective outcome reporting bias.

Conclusions—LTRAs as monotherapy improved asthma control compared to placebo. It remains unclear however, which patients with asthma are more likely to respond to treatment with LTRAs.

Introduction

Asthma is one of the most common chronic diseases with considerable social and economic burdens, involving both high direct costs related to healthcare utilization and indirect costs related to time lost from work or school (1). In the US the annual cost is estimated around \$56 billion. Approximately 300 million people worldwide, and 25 million Americans, are affected by asthma. Worldwide, the number is expected to rise to 400 million by 2025 (2).

The successful long-term management of asthma includes the use of medications that target the underlying inflammatory process. Although inhaled corticosteroids (ICS) constitute the current gold standard of maintenance treatment, leukotriene receptor antagonists (LTRAs) have the advantages of oral once or twice daily dosing and, apparent avoidance of the adverse effects associated with long-term corticosteroid therapy (3). In addition, their mechanism of action theoretically predicts a good response in patients with specific asthma “phenotypes”. Allergic rhinitis (AR) is present in many patients with asthma and LTRAs might improve asthma-related outcomes by treating both conditions concurrently (4). Moreover, aspirin-induced asthma (AIA), which is clinically characterized by chronic eosinophilic rhinosinusitis, nasal polyposis, aspirin hypersensitivity, and development of persistent asthma, is associated with increased airway leukotrienes and is frequently poorly

responsive to ICS (5). Current guidelines recommend the use of LTRAs as monotherapy in patients with mild persistent asthma, as an alternative, or as add-on therapy to ICS, and as an alternative to either increasing the ICS dose or adding a long-acting β_2 -agonist (6). However, the relative benefits and harms of LTRAs compared with placebo have not been established.

We conducted a systematic review of randomized controlled trials (RCTs) that compared the efficacy and safety of LTRAs with placebo in adults and adolescents with asthma for both objective and patient-reported outcome measures used to assess asthma control.

Methods

Data sources and search

We searched MEDLINE and the Cochrane Central Register of Controlled trials from inception through June 2015. We developed a search strategy with a combination of Medical Subject Headings terms and keywords relevant to study design (“randomized controlled trial”), disease of interest (“asthma”), and intervention of interest (“leukotriene receptor antagonists”) [Appendix Table 1].

Study selection

We included peer-reviewed publications of RCTs if they fulfilled the following criteria: comparison of a LTRA either as monotherapy or as add-on therapy to ICS with placebo in adults and adolescents (≥ 12 years) with asthma; oral administration of usual licensed doses of a LTRA on a daily basis (montelukast 10 mg once daily for individuals ≥ 15 years, zafirlukast 20 mg twice daily for individuals ≥ 12 years, pranlukast 225 mg twice daily for individuals ≥ 12 years); minimum treatment duration of 4 weeks; inclusion of at least one pre-specified outcome measure that reflects asthma control (asthma exacerbations, pulmonary function tests, daytime asthma symptom scores, asthma-specific quality of life, nocturnal awakenings, short acting β_2 -agonist use, adverse events); and English language publication. The primary outcome measure was the number of exacerbations that required systemic corticosteroids, an unscheduled visit to a doctor, or a visit to an emergency department. Asthma-specific quality of life was assessed using the asthma-specific quality of life and mini asthma quality of life questionnaires (7, 8). The scales range from 1 to 7 (or 0 to 6), with higher values indicating better quality of life; the minimally important difference considered clinically important is 0.5 (7, 8). Due to the inclusion of children and adolescents in some studies of montelukast, we included studies in which at least some children and adolescents received 10 mg montelukast daily and excluded those in which none of the participants received 10 mg. Two investigators (M.M. and H.A.) independently reviewed the titles and abstracts of the citations for potentially relevant articles using Abstrackr (9); the full text publications of potentially relevant articles were retrieved and rescreened by the same two investigators. Disagreements were resolved by consensus.

Data Extraction and quality assessment

Data from each eligible study were independently extracted by two of three investigators (M.M., H.A., R.B.); any disagreements were resolved by consensus. We extracted data on

study design and methodology, patient characteristics, interventions, comparators, outcome measures, and adverse events using a standardized electronic form in the Systematic Review Data Repository (SRDR) (10).

We assessed the methodological quality of the eligible studies using the Cochrane Collaboration's Risk of Bias tool for randomized trials (11). This tool includes 13 risk of bias items (Appendix Table 2). A judgment of 'low', 'high', or 'unclear' risk of bias was assigned for the first seven items (sequence generation, allocation concealment, patients' blinding, caregivers' blinding, outcome assessors' blinding, attrition, selective outcome reporting), whereas a judgment of 'yes', 'no', or 'unsure' was assigned for the remainder (intention-to-treat analysis, baseline balance, co-interventions similarity, compliance, presence of other biases). Reviewing across all risk of bias items, we assigned an overall quality grade of good, fair, or poor to each RCT. We considered a study of poor quality if any of the following was observed: a) absence of blinding, b) differential loss-to-follow up, c) baseline imbalances, d) absence of a washout period in the case of crossover trials. Studies that reported sufficient details about the implementation of blinding (e.g., double-blind and use of identical capsules) were considered as having low risk of bias for this specific item, whereas studies with insufficient reporting (e.g., double-blind) were considered as having unclear risk of bias. We compared the proportions of withdrawals in each group using the Chi-square test and a p-value less than 0.1 was indicative of differential loss-to-follow up. The assessments were completed by one author (M.M.).

Data Synthesis and Analysis

Study treatment effects for binary outcomes were estimated using the risk ratio (RR) with corresponding 95% confidence intervals (CI). For the continuous outcome measures, the difference in mean changes from baseline between LTRAs and placebo was calculated for each study. Study treatment effects for daytime symptom scores and asthma-specific quality of life scores were computed using Hedges' g statistic corrected for small samples (12). When only the baseline and final SDs were reported, we calculated SDs of change from baseline in each group assuming a correlation coefficient of 0.5 (13). When means and measures of dispersion were not reported in the text, they were approximated from figures using Engauge Digitizer Qt4 (14). We imputed missing group SDs in one study (and for one outcome measure) using the median of all available SDs from other studies, which were measured on the same scale.

In the meta-analyses, the summary treatment effects were estimated using the random-effects model estimated by the empirical Bayes method (15). We calculated a summary RR, a summary mean difference (MD), and a summary standardized mean difference (SMD) between LTRAs and placebo, where appropriate. Statistical heterogeneity was assessed by the I^2 statistic (16). Cross-over trials were included in the analyses only if they provided appropriate data in order to approximate a paired analysis. The overall analysis included only the reported endpoint values at the longest follow-up within each trial. We explored the effect of pre-specified factors on the effect estimates with random effects model meta-regression when an outcome of interest was reported by at least three RCTs in each subgroup. The pre-specified factors were: type of LTRA, treatment duration, asthma

severity, presence of comorbid allergic rhinitis and aspirin-induced asthma. The RCTs were classified into two categories based on the concomitant use of ICS in the intervention groups; LTRA monotherapy (i.e., no ICS use), LTRA as add-on to ICS (i.e., concomitant ICS use either by all patients or by a proportion of patients in the intervention groups). Posthoc sensitivity analyses were performed excluding studies of poor reporting quality. Since the treatment duration varied among the trials, we grouped the time points of outcome assessments in the individual trials into six intervals: 4–7, 8–11, 12–15, 16–23, 24–30, and >30 weeks. This grouping was designed to best capture all available data in the trials, but also reflects periodic monitoring of asthma control used in clinical practice (17). All analyses were performed with OpenMetaAnalyst (18).

Role of the funding source

The funding source had no role in the design or conduct of the present study.

Results

Literature search

Figure 1 summarizes our search yield. We screened 2008 citations. A total of 135 articles were retrieved for full-text review, of which 50 RCTs met our inclusion criteria (19–68).

Trial characteristics

Table 1 summarizes the characteristics of the included RCTs, which were published between 1994 and 2014. Five RCTs included both children and adolescents (53, 56–58, 60) and one RCT included both children and adults (27). Asthma was generally diagnosed by the demonstration of reversibility of airway obstruction after administration of short-acting β_2 -agonists. Definitions of asthma severity categories varied between trials. The main exclusion criteria within trials were active upper respiratory tract infection, recent use of oral corticosteroids, and recent emergency room visit or hospitalization due to worsening asthma.

Overall, 9872 patients were randomized to receive either a LTRA or placebo. Montelukast was administered in 36 RCTs, zafirlukast in 9, and pranlukast in 5. LTRA was used solely as monotherapy by 25 trials. ICS were used as concomitant treatments by all patients in 16 trials, whereas in 8 trials ICS were used only by a proportion of participants. In four RCTs, the dose of ICS was gradually reduced during follow-up according to specific criteria described in the trials. Short-acting β_2 -agonists were permitted on an “as needed” basis in all trials. Mean FEV₁ at baseline was between 59% and 102% of predicted values. Sixteen RCTs reported inclusion of patients with a history of atopy, 11 reported presence of concomitant allergic rhinitis, and two RCTs reported inclusion of patients with aspirin-induced asthma. Patients with exercise induced bronchoconstriction were included in five trials. There were 41 parallel and 9 crossover RCTs. Twenty-nine RCTs were multicenter. Treatment duration ranged from 4 to 30 weeks. Appendix Table 3 lists all included trials and shows which studies contributed data to the meta-analysis of each outcome.

Assessment of risk of bias

Among the 50 RCTs, 22 were assessed to be of good quality, 13 of fair quality, and 15 of poor quality (Appendix Table 4). Generation of a randomized sequence and allocation concealment were not clearly reported in the majority of trials. All but one RCT reported double-blinding; the other RCT was single-blind. Six RCTs had differential loss-to-follow-up. Intention-to-treat analyses were not widely used. RCTs were generally balanced with regard to baseline characteristics and co-interventions. Among the nine crossover trials, six had at least a 1-week washout period which was considered adequate; one had no washout period and two did not clarify whether a washout period was implemented.

Studies not included in the meta-analyses

A summary of the results from the trials included in the systematic review, but not meta-analyzed, is presented in Appendix Table 5. In general, the main reasons of exclusion from meta-analysis concerned inadequate reporting (e.g., reporting only non-significance of difference in effects) or missing data (e.g., missing effect estimates). In addition, six crossover trials were not included in the meta-analyses. These RCTs either did not provide appropriate data in order to approximate a paired analysis or data from the first and second period were provided separately. However, the majority of the excluded RCTs reported statistically non-significant results for the secondary outcomes of interest.

Asthma Exacerbations

In the present analysis, we only included RCTs that had clear and pre-specified criteria of asthma exacerbation. Four trials that reported only withdrawals due to an exacerbation that required either oral corticosteroids or emergency room visit were not quantitatively summarized.

In six RCTs of LTRA monotherapy (with no ICS use), the definition of an exacerbation was consistent with our definition. This analysis included 1703 patients who received a LTRA and 1124 patients who received placebo. Overall, patients treated with LTRAs as monotherapy displayed a 40% decreased risk of experiencing an exacerbation compared to those treated with placebo (summary RR = 0.60; 95% CI 0.44, 0.81) (Figure 2). The observed statistical heterogeneity was moderate ($I^2 = 34\%$). The effect of treatment duration on the summary estimate could not be assessed due to the limited number of RCTs of no ICS use. Similarly, we could not assess the impact of the type of LTRA on the summary estimate because montelukast was administered in four RCTs and zafirlukast in only two trials. We could not examine the effect of allergic rhinitis or aspirin-induced asthma on the summary estimate due to incomplete reporting in the RCTs included.

In four RCTs of LTRA as add-on to ICS, the definition of an exacerbation was consistent with our definition (one RCT included two separate comparisons of LTRA vs. placebo in different patients). In only one RCT were all patients receiving ICS; in three RCTs only some (25–75%) patients received ICS. There was no statistically significant difference in the risk of exacerbations between the intervention groups (summary RR = 0.80; 95% CI: 0.60, 1.07). Statistical heterogeneity was low ($I^2=16\%$).

The results from the meta-analyses of the secondary outcome measures are presented in detail in Table 2.

Forced Expiratory Volume in one second (FEV₁)

Forty-five trials reported the effect of LTRAs compared with placebo on FEV₁. Thirty-seven trials reported FEV₁ in liters (L) and 16 as percent of predicted values (FEV₁ % predicted). A mean difference in change from baseline in FEV₁ (L) was computed for eight trials of no ICS use and nine trials of equal ICS use, a mean difference in percent change from baseline was computed for six trials of no ICS use and five trials of equal ICS use, and a mean difference in FEV₁ % predicted was computed for nine trials of no ICS use and four trials of equal ICS use.

In the trials of LTRA monotherapy, LTRAs significantly improved FEV₁ (L) and FEV₁ % predicted [Appendix Figures 1-3. Meta-regression showed no association between treatment duration and the pooled effect for FEV₁ (L) ($p = 0.11$) [Appendix Figure 4]. We did not observe any significant difference in the effect of zafirlukast compared to montelukast ($p = 0.32$). [Appendix Figure 5]. In the trials of LTRA used as an add-on to ICS, LTRAs significantly improved FEV₁ (L), but not FEV₁ % predicted, compared to placebo [Appendix Figures 6–8]. There was no association between treatment duration and the pooled effect for FEV₁ (L) ($p = 0.71$) [Appendix Figure 9]. The limited number of studies precluded meta-regression of the pre-specified factors for FEV₁ % change from baseline and FEV₁ % predicted.

Daytime symptoms

Daytime symptom scores were reported in 23 RCTs. Seven trials of LTRA monotherapy and eight trials of LTRA add-on use contributed data to the meta-analyses. A variety of scales were used with lower values indicating fewer symptoms. LTRAs significantly reduced daytime symptoms in trials of LTRA used as an add-on to ICS, whereas the reduction did not reach statistical significance in trials of LTRA monotherapy (Appendix Figures 10, 11).

Short acting β 2-agonist use (SABA)

The effect of LTRAs on short acting β 2-agonist use compared to placebo was examined in 30 RCTs. We could compute a mean difference in change from baseline in β -agonist use for eight trials of LTRA monotherapy and five trials of LTRA used as add-on to ICS. Similarly, a mean difference in percent change from baseline was computed for six trials of LTRA monotherapy and three trials of LTRA add-on use. Overall, LTRAs reduced β -agonist use (Appendix Figures 12–15).

Nocturnal awakenings

Nocturnal awakenings were reported in 15 RCTs. Only six RCTs of LTRA monotherapy and two RCTs of LTRA used as add-on to ICS could be meta-analyzed due to missing data in the original trials (primarily, missing number of participants analyzed). Overall, LTRAs reduced nocturnal awakenings per week (Appendix Figures 16, 17).

Asthma-specific quality of life (ASQL)

Eleven trials examined the effect of LTRAs compared to placebo on asthma-specific quality of life. However, only four trials (one RCT included two independent comparisons) of LTRA add-on use contributed data to our meta-analysis. There was only one trial of LTRA monotherapy. LTRAs did not improve quality of life compared to placebo (Appendix Figure 18).

Sensitivity analyses

Overall, seven trials of poor quality were included in the meta-analyses. In five trials of no ICS use, LTRAs significantly reduced asthma exacerbations (summary RR = 0.60, 95% CI: 0.40, 0.90, $I^2 = 46\%$) and in three trials of equal ICS use, we observed similar results to our main analysis (summary RR = 0.79, 95% CI: 0.52, 1.20, $I^2 = 32\%$). For the secondary outcomes of interest, the exclusion of RCTs of poor quality did not significantly alter the results (Appendix Table 6).

Likewise, the exclusion of two cross over trials with no washout period from the respective meta-analyses had no impact on the results (Appendix Table 6).

Adverse events and tolerability

The proportions of patients with adverse events were generally similar between intervention and comparator groups (Appendix Table 7). Across all trials, no serious adverse events were reported. Five trials explicitly reported no adverse events. Withdrawals from adverse events or worsening asthma were generally similar across groups (Appendix Table 8).

Discussion

Administration of a LTRA to adults and adolescents with asthma significantly reduced the risk of an exacerbation. In trials of LTRA monotherapy, LTRAs significantly improved asthma control compared with placebo, whereas only some measures of asthma control were significantly improved in trials of LTRA add-on use to ICS. This effect was consistent across all types of LTRAs. The incidence of adverse events and withdrawals due to adverse events and worsening asthma was similar for LTRAs and placebo reflecting a favorable safety and tolerability profile for LTRAs.

Several systematic reviews have examined the state of evidence regarding the use of LTRAs in adults and adolescents with asthma, but only a few have included RCTs that compared a LTRA with placebo. Joos et al. (68) included RCTs of at least 12 weeks duration that examined the benefits and harms of montelukast as add-on therapy to ICS compared to ICS with or without placebo and concluded that the addition of montelukast to ICS improved control of mild to moderate asthma compared to ICS monotherapy. No meta-analytic technique was employed in this study, however, due to the inclusion of a limited number of RCTs. Ducharme et al. (69) included RCTs of at least 4 weeks duration that compared LTRAs with placebo as add-on to ICS, but only two of the six included RCTs reported use of usual licensed doses. Currie et al. (70) examined the bronchoprotective effects of LTRAs compared to placebo after administration of bronchial stimuli. These provocative challenges,

though, are mainly used in order to establish the diagnosis of asthma. In contrast, our systematic review was more expansive and more applicable to current clinical practice in a number of ways. Our study included outcome measures that correspond to the components proposed by international guidelines to periodically assess and monitor asthma control in patients with an established diagnosis of asthma (71). More specifically, we included RCTs of at least 4 weeks duration because the level of asthma control is assessed over a 4 week period at the minimum (6). We also excluded RCTs where LTRAs were not administered on a daily basis because we intended to examine their effect as long-term controller medications (6). Therefore, RCTs that only assessed the pharmacodynamic profile of single doses of LTRAs after provocative challenges or exercise were excluded. In a systematic review of LTRA safety data that included both RCTs and their extension studies, Storms et al. (72) concluded that there was no significant difference in the incidence of adverse events between patients who were treated with montelukast and those who received placebo. Although our systematic review included only RCTs with a relatively short length of follow-up, the reported adverse events and their relative frequencies were similar to those reported in the meta-analysis by Storms et al.

Despite the broader scope and improved generalizability of our study to previous reviews, our systematic review had several limitations both at the individual-study level and the systematic review level that need to be kept in mind in interpreting our study results. Different definitions of asthma exacerbation were used in the trials and some studies did not explicitly define it. Consequently, the severity of the exacerbations could not be fully assessed across studies. Therefore, due to the clinical importance of our specific definition of an asthma exacerbation, we only meta-analyzed studies that clearly defined and reported the outcome and we did not quantitatively summarize twelve studies (four with a definition consistent definition with ours) which reported only withdrawals because the number of patients at risk could not be determined (i.e., absence of any pre-specified criteria for withdrawal due to an exacerbation). In addition, the definitions of asthma severity in the individual trials were not consistent and it was not possible to assess the impact of baseline asthma severity on summary treatment effects. Nevertheless, the use of ICS in some trials may indicate that patients with more severe disease were included in those. Our conclusions about the magnitude of the treatment effect are limited due to the small number of RCTs included in each analysis compared to the total number of RCTs included in the systematic review. Part of this difference arises because studies used different analytic scales for the same outcome measure, which prevented combination of all available data. For instance, change from baseline in FEV₁ was provided as an absolute number in some trials and as a percentage in others. Another set of studies reported a non-significant difference, without providing the actual numbers, for clinical outcomes. These studies were generally either not primarily designed to assess outcome measures relevant to clinical practice or had a relatively small sample size. In either case, this leads to outcome reporting bias and so the summary effect sizes from the meta-analyses may be overstated.

The observed between-study statistical heterogeneity found for most outcomes remained largely unexplained, partly due to the limited number of trials included in each analysis. Potential association between allergic rhinitis and the magnitude of the summary treatment effect remains unclear due to insufficient reporting in the individual studies. Moreover, no

subgroup analyses in the individual studies were reported. Similarly, only two trials reported inclusion of patients with aspirin-induced asthma. Finally, another limitation of the study is the inclusion of only peer-reviewed and English-language publications and therefore we cannot exclude publication bias.

This systematic review investigates the use of all marketed LTRAs in usual licensed doses as asthma controller medications compared with placebo. Our findings suggest that LTRAs might be an efficacious and safe either alternative treatment, in adult and adolescent patients who cannot or prefer not to take ICS or add-on treatment, in patients with concomitant ICS use. However, which patients are more likely to respond to LTRAs remains unclear. Asthma is a complex disease with various clinical, inflammatory, and trigger-related phenotypes that may overlap (73). It is hypothesized that proper identification of these phenotypes would lead to better management of the disease. Moreover, since not all patients respond well to ICS, the need for alternative treatments that would benefit specific subpopulations increases. Therefore, professional organizations or expert panels should recommend standardized study-protocols, definitions of phenotypes, and outcome measures (e.g., asthma control test, asthma control questionnaire) (74, 75) for the purpose of research and encourage future researchers to implement these standards.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Asthma and Allergy Foundation. [Accessed February 15, 2013] The costs of asthma. 1992 and 1998 Study, 2000 Update <http://www.aafa.org/>
2. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*. 2004 May; 59(5):469–78. [PubMed: 15080825]
3. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. *Am J Med*. 1995 Feb; 98(2):196–208. [PubMed: 7847437]
4. Philip G, Nayak AS, Berger WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin*. 2004 Oct; 20(10):1549–58. [PubMed: 15462688]
5. European Network for Understanding Mechanisms of Severe Asthma. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J*. 2003; 22:470–77. [PubMed: 14516137]
6. From the Global Strategy for Asthma Management and Prevention. [Accessed May 10, 2015] Global Initiative for Asthma (GINA). 2012. Available from <http://www.ginasthma.org/>
7. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax*. 1992 Feb; 47(2):76–83. [PubMed: 1549827]

8. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J*. 1999 Jul; 14(1):32–8. [PubMed: 10489826]
9. Wallace, BC.; Small, K.; Brodley, C.; Lau, J.; Trikalinos, TA. Deploying an interactive machine learning system in an evidence-based practice center: abstrackr [Abstract]. Proceedings of the Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium; Miami, Florida, 28030. January; New York: Assoc Computing Machinery; 2012. p. 819-24. Available from <http://abstrackr.cebm.brown.edu/>
10. Ip S, Hadar N, Keefe S, et al. A Web-based archive of systematic review data. *Syst Rev*. 2012 Feb 21;1(1):15. [PubMed: 22588052]
11. Higgins, JPT.; Altman, DG. Assessing risk of bias in included studies. In: Higgins, JPT.; Green, S., editors. *Cochrane handbook for systematic reviews of interventions*. Wiley; 2008. p. 187-241.
12. Cooper, H.; Hedges, LV., editors. *The hand book of research synthesis*. 1. New York: Russell Sage Foundation; 1994.
13. Balk, EM.; Earley, A.; Patel, K.; Trikalinos, TA.; Dahabreh, IJ. Empirical Assessment of Within-Arm Correlation Imputation in Trials of Continuous Outcomes. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012. Nov. Report No.: 12(13) –EHC141-EF. AHRQ Methods for Effective Health Care
14. [Accessed February 2015] Digitizing software. Available from <http://digitizer.sourceforge.net/>
15. Raudenbush SW, Bryk AS. Empirical Bayes meta-analysis. *J Educ Stat*. 1985 Sep; 10(2):75–98.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003 Sep 6; 327(7414):557–60. [PubMed: 12958120]
17. Murphy, S.; Sheffer, AL.; Pauwels, R. National Institutes of Health publication 97–4051. Bethesda, MD: National Heart, Lung and Blood Institute; 1997. National asthma education and prevention program. Expert panel report 2: guidelines for the diagnosis and management of asthma.
18. [Accessed May 14, 2015] OpenMetaAnalyst: Powerful Open-Source Software for Meta-Analysis. Available from http://www.cebm.brown.edu/open_meta/
19. Altman LC, Munk Z, Seltzer J, et al. A placebo-controlled, dose-ranging study of montelukast, a cysteinyl leukotriene-receptor antagonist. Montelukast Asthma Study Group. *J Allergy Clin Immunol*. 1998 Jul; 102(1):50–6. [PubMed: 9679847]
20. American Lung Association Asthma Clinical Research Center. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. *Am J Respir Crit Care Med*. 2007 Feb 1; 175(3):235–42. [PubMed: 16998094]
21. Awad N, Joshi J, Naidu MUR, et al. Comparative evaluation of the efficacy of zafirlukast 20mg tablets versus placebo in Patients with mild to moderate asthma. *Indian Pract*. 2002; 55(5):303–321.
22. Baena-Cagnani CE, Berger WE, DuBusse LM, et al. Comparative effects of desloratadine versus montelukast on asthma symptoms and use of beta 2-agonists in patients with seasonal allergic rhinitis and asthma. *Int Arch Allergy Immunol*. 2003 Apr; 130(4):307–13. [PubMed: 12740532]
23. Barnes NC, Pujet JC. Pranlukast, a novel leukotriene receptor antagonist: results of the first European, placebo controlled, multicentre clinical study in asthma. *Thorax*. 1997 Jun; 52(6):523–7. [PubMed: 9227718]
24. Baumgartner RA, Martinez G, Edelman JM, et al. Distribution of therapeutic response in asthma control between oral montelukast and inhaled beclomethasone. *Eur Respir J*. 2003 Jan; 21(1):123–8. [PubMed: 12570120]
25. Busse W, Wolfe J, Storms W, et al. Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. *J Fam Pract*. 2001 Jul; 50(7):595–602. [PubMed: 11485708]
26. Cakmak G, Demir T, Gemiciglu B, Aydemir A, Serdaroglu E, Donma O. The effects of add-on zafirlukast treatment to budesonide on bronchial hyperresponsiveness and serum levels of eosinophilic cationic protein and total antioxidant capacity in asthmatic patients. *Tohoku J Exp Med*. 2004 Dec; 204(4):249–56. [PubMed: 15572850]

27. Capriles Hulett A, Yibirin MG, Garcia A, Hurtado D. Montelukast for the high impact of asthma exacerbations in Venezuela: a practical and valid approach for Latin America? *World Allergy Organization Journal*. 2014; 7:20. [PubMed: 25232371]
28. Dahlén SE, Malmström K, Nizankowska E, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002 Jan 1; 165(1):9–14. [PubMed: 11779723]
29. Fish JE, Kemp JP, Lockey RF, Glass M, Hanby LA, Bonuccelli CM. Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. The Zafirlukast Trialists Group. *Clin Ther*. 1997 Jul-Aug;19(4):675–90. [PubMed: 9377612]
30. Gao JM, Cai F, Peng M, Ma Y, Wang B. Montelukast improves air trapping, not airway remodeling, in patients with moderate-to-severe asthma: a pilot study. *Chin Med J (Engl)*. 2013 Jun; 126(12):2229–34. [PubMed: 23786930]
31. Green RH, Brightling CE, McKenna S, et al. Comparison of asthma treatment given in addition to inhaled corticosteroids on airway inflammation and responsiveness. *Eur Respir J*. 2006 Jun; 27(6): 1144–51. [PubMed: 16455831]
32. Helenius I, Lumme A, Ounap J, et al. No effect of montelukast on asthma-like symptoms in elite ice hockey players. *Allergy*. 2004 Jan; 59(1):39–44. [PubMed: 14674932]
33. Huang CJ, Wang CH, Liu WT, et al. Zafirlukast improves pulmonary function in patients with moderate persistent asthma receiving regular inhaled steroids: a prospective randomized control study. *Chang Gung Med J*. 2003 Aug; 26(8):554–60. [PubMed: 14609035]
34. Israel E, Chervinsky PS, Friedman B, et al. Effects of montelukast and beclomethasone on airway function and asthma control. *J Allergy Clin Immunol*. 2002 Dec; 110(6):847–54. [PubMed: 12464949]
35. Jayaram L, Duong M, Pizzichini MM, et al. Failure of montelukast to reduce sputum eosinophilia in high-dose corticosteroid-dependent asthma. *Eur Respir J*. 2005 Jan; 25(1):41–6. [PubMed: 15640321]
36. Jayaram L, Pizzichini E, Lemièrre C, et al. Steroid naive eosinophilic asthma: anti-inflammatory effects of fluticasone and montelukast. *Thorax*. 2005 Feb; 60(2):100–5. [PubMed: 15681495]
37. Kanazawa H, Yoshikawa T, Hirata K, Yoshikawa J. Effects of pranlukast administration on vascular endothelial growth factor levels in asthmatic patients. *Chest*. 2004 May; 125(5):1700–5. [PubMed: 15136379]
38. Kannies F, Richter K, Janicki S, Schleiss MB, Jörres RA, Magnussen H. Dose reduction of inhaled corticosteroids under concomitant medication with montelukast in patients with asthma. *Eur Respir J*. 2002 Nov; 20(5):1080–7. [PubMed: 12449158]
39. Kraft M, Cairns CB, Ellison MC, Pak J, Irvin C, Wenzel S. Improvements in distal lung function correlate with asthma symptoms after treatment with oral montelukast. *Chest*. 2006 Dec; 130(6): 1726–32. [PubMed: 17166989]
40. Laviolette M, Malmstrom K, Lu S, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. *Am J Respir Crit Care Med*. 1999 Dec; 160(6):1862–8. [PubMed: 10588598]
41. Leff JA, Busse WW, Pearlman D, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med*. 1998 Jul 16; 339(3):147–52. [PubMed: 9664090]
42. Löfdahl CG, Reiss TF, Leff JA, et al. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. *BMJ*. 1999 Jul 10; 319(7202):87–90. [PubMed: 10398629]
43. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med*. 1999 Mar 16; 130(6):487–95. [PubMed: 10075616]
44. Minoguchi K, Kohno Y, Minoguchi H, et al. Reduction of eosinophilic inflammation in the airways of patients with asthma using montelukast. *Chest*. 2002 Mar; 121(3):732–8. [PubMed: 11888953]

45. Nakamura Y, Hoshino M, Sim JJ, Ishii K, Hosaka K, Sakamoto T. Effect of the leukotriene receptor antagonist pranlukast on cellular infiltration in the bronchial mucosa of patients with asthma. *Thorax*. 1998 Oct; 53(10):835–41. [PubMed: 10193369]
46. Nathan RA, Bernstein JA, Bielory L, et al. Zafirlukast improves asthma symptoms and quality of life in patients with moderate reversible airflow obstruction. *J Allergy Clin Immunol*. 1998 Dec; 102(6 Pt 1):935–42. [PubMed: 9847434]
47. Nathan RA, Minkwitz MC, Bonuccelli CM. Two first-line therapies in the treatment of mild asthma: use of peak flow variability as a predictor of effectiveness. *Ann Allergy Asthma Immunol*. 1999 May; 82(5):497–503. [PubMed: 10353583]
48. Nathan RA, Yancey SW, Waitkus-Edwards K, et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest*. 2005 Oct; 128(4):1910–20. [PubMed: 16236835]
49. Pizzichini E, Leff JA, Reiss TF, et al. Montelukast reduces airway eosinophilic inflammation in asthma: a randomized, controlled trial. *Eur Respir J*. 1999 Jul; 14(1):12–8. [PubMed: 10489822]
50. Price D, Popov TA, Bjermer L, et al. Effect of montelukast for treatment of asthma in cigarette smokers. *J Allergy Clin Immunol*. 2013 Mar; 131(3):763–71. [PubMed: 23380218]
51. Reid DW, Misso NL, Aggarwal S, Thompson PJ, Johns DP, Walters EH. Tolerance and rebound with zafirlukast in patients with persistent asthma. *J Negat Results Biomed*. 2008 May 19;7:3. [PubMed: 18489783]
52. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. *Arch Intern Med*. 1998 Jun 8; 158(11):1213–20. [PubMed: 9625400]
53. Schäper C, Noga O, Koch B, et al. Anti-inflammatory properties of montelukast, a leukotriene receptor antagonist in patients with asthma and nasal polyposis. *J Investig Allergol Clin Immunol*. 2011; 21(1):51–8.
54. Spahn JD, Covar RA, Jain N, et al. Effect of montelukast on peripheral airflow obstruction in children with asthma. *Ann Allergy Asthma Immunol*. 2006 Apr; 96(4):541–9. [PubMed: 16680924]
55. Spector SL, Smith LJ, Glass M. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D4 receptor antagonist, in subjects with bronchial asthma. ACCOLATE Asthma Trialists Group. *Am J Respir Crit Care Med*. 1994 Sep; 150(3):618–23. [PubMed: 8087328]
56. Spector SL, Tan RA. Effectiveness of montelukast in the treatment of cough variant asthma. *Ann Allergy Asthma Immunol*. 2004 Sep; 93(3):232–6. [PubMed: 15478381]
57. Stelmach I, Grzelewski T, Bobrowska-Korzeniowska M, Stelmach P, Kuna P. A randomized, double-blind trial of the effect of anti-asthma treatment on lung function in children with asthma. *Pulm Pharmacol Ther*. 2007; 20(6):691–700. [PubMed: 17046300]
58. Stelmach I, Jerzynska J, Kuna P. A randomized, double-blind trial of the effect of glucocorticoid, antileukotriene and beta-agonist treatment on IL-10 serum levels in children with asthma. *Clin Exp Allergy*. 2002 Feb; 32(2):264–9. [PubMed: 11929492]
59. Stelmach I, Jerzynska J, Kuna P. A randomized, double-blind trial of the effect of treatment with montelukast on bronchial hyperresponsiveness and serum eosinophilic cationic protein (ECP), soluble interleukin 2 receptor (sIL-2R), IL-4, and soluble intercellular adhesion molecule 1 (sICAM-1) in children with asthma. *J Allergy Clin Immunol*. 2002 Feb; 109(2):257–63. [PubMed: 11842294]
60. Storms W, Chervinsky P, Ghannam AF, Bird S, Hustad CM, Edelman JM. Challenge-Rescue Study Group. A comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. *Respir Med*. 2004 Nov; 98(11):1051–62. [PubMed: 15526805]
61. Strunk RC, Bacharier LB, Phillips BR, et al. Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderate-to-severe childhood asthma study. *J Allergy Clin Immunol*. 2008 Dec; 122(6):1138–1144. [PubMed: 18951618]

62. Tohda Y, Fujimura M, Taniguchi H, et al. Leukotriene receptor antagonist, montelukast, can reduce the need for inhaled steroid while maintaining the clinical stability of asthmatic patients. *Clin Exp Allergy*. 2002 Aug; 32(8):1180–6. [PubMed: 12190656]
63. Ulrik CS, Diamant Z. *Allergy Asthma Proc*. 2009; 30(1):64–68. [PubMed: 19331721]
64. Vaquerizo MJ, Casan P, Castillo J, et al. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax*. 2003 Mar; 58(3):204–10. [PubMed: 12612294]
65. Wise RA, Bartlett SJ, Brown ED, et al. Randomized trial of the effect of drug presentation on asthma outcomes: the American Lung Association Asthma Clinical Research Centers. *J Allergy Clin Immunol*. 2009 Sep; 124(3):436–44. [PubMed: 19632710]
66. Yoo SH, Park SH, Song JS, et al. Clinical effects of pranlukast, an oral leukotriene receptor antagonist, in mild-to-moderate asthma: a 4 week randomized multicentre controlled trial. *Respirology*. 2001 Mar; 6(1):15–21. [PubMed: 11264758]
67. Yoshida S, Ishizaki Y, Shoji T, et al. Effect of pranlukast on bronchial inflammation in patients with asthma. *Clin Exp Allergy*. 2000 Jul; 30(7):1008–14. [PubMed: 10848924]
68. Zeidler MR, Kleerup EC, Goldin JG, et al. Montelukast improves regional air-trapping due to small airways obstruction in asthma. *Eur Respir J*. 2006 Feb; 27(2):307–15. [PubMed: 16452585]
69. Joos S, Miksch A, Szecsenyi J, et al. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. *Thorax*. 2008 May; 63(5):453–62. [PubMed: 18443162]
70. Ducharme FM. Anti-leukotrienes as add-on therapy to inhaled glucocorticoids in patients with asthma: systematic review of current evidence. *BMJ*. 2002 Jun 29; 324(7353):1545. [PubMed: 12089089]
71. Currie GP, Lipworth BJ. Bronchoprotective effects of leukotriene receptor antagonists in asthma: a meta-analysis. *Chest*. 2002 Jul; 122(1):146–50. [PubMed: 12114350]
72. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007 Nov; 120(5 Suppl):S94–138. [PubMed: 17983880]
73. Storms W, Michele TM, Knorr B, et al. Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged > or = 6 years. *Clin Exp Allergy*. 2001 Jan; 31(1):77–87. [PubMed: 11167954]
74. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet*. 2006 Aug 26; 368(9537):804–13. [PubMed: 16935691]
75. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004 Jan; 113(1):59–65. [PubMed: 14713908]

Figure 1.
Flow diagram

Figure 2.

Summary forest plot for asthma exacerbation.

Meta-analyses of the overall risk ratio (yellow diamonds) were conducted separately for LTRA monotherapy vs. placebo (top) and LTRA as an add-on to ICS vs. placebo and ICS (bottom). The size of the squares representing each study's effect size is proportional to the weight of each study in the meta-analysis. Also note that the P value is for chi-squared heterogeneity.

Ev/LTRA = Events/Total number of patients with exacerbation in the LTRA group. Ev/Placebo = Events/Total number of patients with exacerbation in the Placebo group.

Trial characteristics

Table 1

Source	Region	Treatment arms	Concomitant treatments	Treatment duration, weeks	Patients, n	Age, years [†]	Sex, %Male	FEV ₁ % predicted at baseline [‡] (SD)	FEV ₁ % predicted range of inclusion
Altman 1998	USA	Montelukast Placebo	Theophylline, ICS*, SABA	6	57 58	33 median 36 median	79 78	62 (13) 59 (13)	40–80
American Lung Association 2007	USA	Montelukast Placebo	ICS*, LABA, SABA	24	164 164	40 40	28 26	77 (17) 80 (16)	> 50
Awad 2002	India	Zafirlukast Placebo	SABA	12	116 99	35 35.	47 50	62 (11) 64 (12)	45–80
Baena-Cagnani 2003	USA	Montelukast Placebo	SABA	4	311 302	34 32	39 33	86 86	> 70
Barnes 1997	Europe	Pranlukast Placebo	BEC* (1000 µg/d), SABA	4	46 44	39 38	59 66	68 (12) 67 (11)	50–80
Baumgartner 2003	North & South America	Montelukast Placebo	SABA	6	313 103	36 36	34 overall	69 (12) 68 (12)	50–85
Busse 2001	USA	Zafirlukast Placebo	SABA	12	111 114	12–75 overall	50 overall	66–67 overall	50–80
Cakmak 2004	Turkey	Zafirlukast/ BUD (400 µg/d) Placebo/ BUD (400µg/d)	SABA	6	11 10	30 28	55 20	88 (14) 89 (14)	70
Capriles Hulett 2014	Venezuela	Montelukast Placebo	ND	24	46 42	18 17	37 36	ND ND	ND
Dahlén 2002	USA, Europe	Montelukast Placebo	Theophylline, ICS*, SABA	4	40 40	49 median 47 median	38 28	70 70	ND

Source	Region	Treatment arms	Concomitant treatments	Treatment duration, weeks	Patients, n	Age, years [†]	Sex, %Male	FEV ₁ % predicted at baseline $\bar{x}$ (SD)	FEV ₁ % predicted range of inclusion
Fish 1997	USA	Zafirlukast Placebo	SABA	13	514 248	18–55 (80%)	57 59	78 (16) 79 (17)	55 et al.
GAO 2013	China	Montelukast Placebo	FCS/LABA (500/100 µg/d)	24	19 19	45.3 48.8	53 42	57 (4) 51 (4)	80
Green 2006	UK	Montelukast/BUD (200µg/d) Placebo / BUD (200 µg/d)	SABA	4	49	42 median	51	75 (3)	ND
Helenius 2004	Finland	Montelukast Placebo	SABA	4	16	18	100	101 (12)	ND
Huang 2003	Taiwan	Zafirlukast Placebo	BUD (800–1600 µg/d), SABA	4	20 18	59 57	53 50	68 (1) 69 (1)	60–80
Israel 2002	USA	Montelukast Placebo	SABA, antihistamines	6	339 111	34 33	48 47	67 (11) 67 (12)	50–80
Jayaram 2005	Canada	Montelukast Placebo	BUD (1857 µg/d), SABA	4	14	61	57	62 (15)	ND
Jayaram 2005	Canada, Brazil	Montelukast Placebo	SABA	8	19 13	31 39	58 71	77 (16) 80 (23)	ND
Kanazawa 2004	Japan	Pranlukast/ BEC (800 µg/d) Placebo/ BEC (800 µg/d)	SABA	4	10	28	60	87	ND
Kanniess 2002	Germany	Montelukast Placebo	BEC (tapered doses), SABA	12	26 24	38 43	50 46	95 (10) 92.3 (9)	> 80
Kraft 2006	USA	Montelukast	SABA	4	19	38	32	83 (3)	ND

Source	Region	Treatment arms	Concomitant treatments	Treatment duration, weeks	Patients, n	Age, years [†]	Sex, %Male	FEV ₁ % predicted at baseline $\bar{x}$ (SD)	FEV ₁ % predicted range of inclusion
		Placebo							et al.
Laviolette 1999	North America, Europe, Africa, Australia, Asia	Montelukast/ BEC (400 µg/d) Placebo/ BEC (400 µg/d) Montelukast Placebo	SABA	16	193 200 201 48	40 median 39 median 38 41	56 52 49 40	72 (12) 71 (12) 72 (12) 71 (11)	50–85
Leff 1998	USA	Montelukast Placebo	SABA, antihistamines	12	54 56	25 25	52 52	83 (11) 84 (11)	ND
Löfdahl 1999	USA, Canada, Europe	Montelukast Placebo	ICS (various doses), SABA	12	113 113	40 41	42 54	85 (11) 82 (13)	> 70
Malmstrom 1999	Europe, Africa, Australia, Central and South America	Montelukast Placebo	Theophylline, SABA	12	387 257	35 median 36 median	40 43	65 (10) 66 (11)	50–85
Minoguchi 2002	Japan	Montelukast Placebo	Theophylline, SABA	4	26	37	50	83 (16)	ND
Nakamura 1998	Japan	Pranlukast Placebo	SABA	4	10 7	35 median 32 median	80 43	71 median 80 median	50
Nathan 1998	USA	Zafirlukast Placebo	SABA, nasal corticosteroids	13	231 223	33 32	45 41	66.6 overall	45–80
Nathan 1999	USA	Zafirlukast Placebo	SABA	13	96 95	32 30	55 53	77 (15) 78 (17)	> 55
Nathan 2005	USA	Montelukast Placebo	FCS/LABA (100/50 µg/d), SABA	4	282 290	34 36	33 28	81 (10) 81 (10)	ND

Source	Region	Treatment arms	Concomitant treatments	Treatment duration, weeks	Patients, n	Age, years [†]	Sex, %Male	FEV ₁ % predicted at baseline $\bar{x}$ (SD)	FEV ₁ % predicted range of inclusion
Pizzichini 1999	USA, Canada	Montelukast Placebo	SABA	4	19 21	31 28	63 57	69 (11) 69 (15)	ND et al.
Price 2013	USA, Europe, Asia, Africa	Montelukast Placebo	SABA	24	347 336	38 38	53 51	74 (10) 74 (9)	60–85
Reid (A) 2008	Australia	Zafirlukast Placebo	SABA	12	14 7	42 median 29 median	57 43	85 80	60
Reid (B)		Zafirlukast/ BUD (1600 µg/d) Placebo/ BUD (1600 µg/d)			16 8	37 median 45 median	56 25	77 76	
Reiss 1998	USA	Montelukast Placebo	ICS*, SABA	12	408 273	31 median 31 median	43 47	67 (11) 69 (11)	50–85
Schäper 2011	Germany	Montelukast Placebo	ICS*, SABA	6	24	56 median	71	88	ND
Spahn 2006	USA	Montelukast Placebo	SABA	8	11 10	13 14	64 36	88 (10) 83 (10)	60–90
Spector 1994	USA	Zafirlukast Placebo	SABA	6	70 70	37 36	74 71	66 69	40–75
Spector 2004	USA	Montelukast Placebo	SABA, nasal corticosteroids	4	8 6	42 36	50 67	> 50	50–85
Stelmach (A) 2007	Poland	Montelukast/ BUD (200µg/d)	ICS/ SABA	4	29	11	69	95 (11)	ND
Stelmach (B)		Placebo/ BUD (200µg/d) Montelukast Placebo			29 29 29	12 10 11	69 62 70	94 (10) 96 (11) 95 (10)	

Source	Region	Treatment arms	Concomitant treatments	Treatment duration, weeks	Patients, n	Age, years [†]	Sex, %Male	FEV ₁ % predicted at baseline $\bar{x}$ (SD)	FEV ₁ % predicted range of inclusion
Stelmach 2002	Poland	Montelukast Placebo	SABA	4	18 36	12 12	60 44	77 (4) 75 (5)	ND
Stelmach 2002	Poland	Montelukast Placebo	SABA	6	16 19	14 13	67 59	85 (9) 81 (7)	ND
Storms 2004	USA	Montelukast/ FCS (200µg/d) Placebo/ FCS (200µg/d)	SABA	4	39 44	33 31	28 45	88 (10) 88 (11)	70
Strunk 2008	USA	Montelukast Placebo	BUD (800–1600µg/d), LABA, SABA	30	19 19	11 overall	58 overall	102 (14)	ND
Tohda 2002	Japan	Montelukast Placebo	BEC (various doses), SABA	24	93 98	16–70 range	58 58	87 (18) 86 (25)	ND
Ulrik 2009	Denmark	Montelukast Placebo	SABA	12	16 15	34 33	44 40	79 (14) 83 (10)	> 70
Vaquerizo 2003	Spain	Montelukast / BUD (400 – 1600µg/d) Placebo/ BUD (400 – 1600µg/d)	SABA	16	326 313	42 44	62 61	81 (19) 81 (21)	55
Wise (A) 2009	USA	Montelukast Placebo	ICS*, SABA	4	120 121	37 39	19 27	87 (12) 87 (15)	> 75
Wise (B)		Montelukast Placebo			119 120	37 39	29 32	86 (13) 87 (13)	
Yoo 2001	South Korea	Pranlukast Placebo	ICS*, SABA	4	98 99	45 45	61 54	73 73	60–80
Yoshida 2002	Japan	Pranlukast Placebo	Theophylline, SABA	4	32	41	44	77 (7)	ND

Source	Region	Treatment arms	Concomitant treatments	Treatment duration, weeks	Patients, n	Age, years [†]	Sex, %Male	FEV ₁ % predicted at baseline [†] (SD)	FEV ₁ % predicted range of inclusion
Zeidler 2006	USA	Montelukast Placebo	SABA	4	20	36	56	86 (12)	60

et al.

Abbreviations: BEC: Beclomethasone; BUD: Budesonide; FCS: Fluticasone; ICS: Inhaled corticosteroids; ND: No data; SABA: Short acting β 2-agonists; SD: Standard deviation.

* ICS used only by a proportion of participants (20%-90%)

[†]Data are shown as means, unless otherwise specified

Table 2

Summary effects of LTRAs versus placebo

Outcome measure	Concomitant ICS use (number of RCTs)	Summary effect (95% CI) *	Heterogeneity (I ²)	Number of poor quality RCTs
FEV₁ (L) change from baseline	No (8)	0.11 (0.06, 0.16)	15%	2
	Equal (9 [†])	0.12 (0.08, 0.15)	48%	2
FEV₁ % change from baseline	No (6)	4.91 (2.13, 7.69)	54%	1
	Equal (5)	7.03 (2.54, 11.53)	80%	1
	Unequal (1)	-2.70 (-7.85, 2.45)	NA	1
FEV₁ % predicted change from baseline	No (9)	6.17 (3.25, 9.10)	68%	2
	Equal (4)	1.35 (-1.46, 4.17)	0%	1
Daytime symptoms change from baseline	No (7)	SMD = -0.21 (-0.54, 0.12)	81%	1
	Equal (8)	SMD = -0.19 (-0.32, -0.06)	29%	1
SABA use (puffs/day) change from baseline	No (8)	-0.67 (-0.85, -0.49)	0%	3
	Equal (5)	-0.61 (-1.05, -0.17)	36%	1
SABA use % change from baseline	No (6)	-21.10 (-36.12, -6.09)	84%	2
	Equal (3)	-12.15 (-18.41, -5.90)	0%	1
Nocturnal awakenings (per week) change from baseline	No (6)	-0.66 (-1.25, -0.07)	83%	3
	Equal (2)	-0.78 (-1.07, -0.49)	0%	0
ASQL change from baseline	No (1)	0.27 (0.11, 0.42)	NA	1
	Equal (4 [†])	SMD = 0.08 (-0.03, 0.18)	0%	0

Abbreviations: ASQL: Asthma-specific quality of life; CI: Confidence interval; FEV₁: Forced expiratory volume in one second; ICS: Inhaled corticosteroids; NA: Not applicable; RCT: Randomized controlled trial; SABA: Short acting β_2 -agonist use; SMD: Standardized mean difference.

* Summary effects are provided as mean differences (MD) unless otherwise specified.

[†] One RCT included two independent comparisons of LTRA versus placebo in different patients.