

REVIEW ARTICLE

Leukotriene receptor antagonists for small-airway abnormalities in asthmatics: a systematic review and meta-analysisXun Chen, MD¹, Ke Wang, MD^{2,3}, Min Jiang, MD¹, and Guang-Min Nong, MD PhD¹¹Department of Paediatrics, and ²Institute of Respiratory Diseases, First Affiliated Hospital of Guangxi Medical University, Nanning, PR China, and³Singapore Centre on Environmental Life Sciences Engineering, Nanyang Technological University, Singapore**Abstract**

Background: Airway inflammation that occurs in asthma is mainly distributed in the small airways. Leukotriene receptor antagonists (LTRAs) are systemically active drugs that may act on the small airways. **Objectives:** The aim of our study was to assess the efficacy of LTRAs for small-airway abnormalities in asthmatics. **Methods:** We searched the databases of Cochrane Central, MEDLINE, and EMBASE from the time of the establishment of the databases to December 2012. The data were extracted using a pooled mean difference (MD) or standardized mean difference (SMD) with a 95% confidence interval (CI). **Results:** Eight studies were included. The outcomes were the conventional parameters for the detection of small-airway abnormalities. Eight studies were included. The outcomes were the conventional parameters for the detection of small-airway abnormalities. LTRAs compared to placebo improved small-airway abnormalities, as indicated by a number of radiological and physiological parameters, such as lung attenuation (MD, 61.00; 95% CI, 26.32 to 95.68) and residual volume (SMD, -0.85; 95% CI, -1.29 to -0.42). Conventional inhaled corticosteroids (ICSs) compared to LTRAs improved small-airway abnormalities, as indicated by the reactance area ($p=0.028$). Compared with conventional treatment alone, a combination of LTRAs and conventional treatment improved small-airway abnormalities, as indicated by a number of radiological and physiological parameters, such as airway wall thickness ($p<0.05$), alveolar nitric oxide concentration ($p=0.04$), a decrease in resistance from 5 to 20 hertz ($p=0.032$), reactance area ($p=0.014$), eosinophil cationic protein levels ($p=0.045$) and number of eosinophils ($p=0.035$) in the late-phase induced sputum. However, there was no significant improvement in forced expiratory flow between 25% and 75% of forced vital capacity in any of the comparisons. **Conclusions:** LTRAs may improve most of the conventional parameters for the detection of small-airway abnormalities in asthmatics. However, there is no evidence of the superiority of LTRAs over ICSs in improving functional parameters related to the small airways.

Keywords

Asthma, inhaled corticosteroid, leukotriene, meta-analysis, parameters, small airway

History

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Introduction**Description of the condition**

Asthma is regarded as a chronic inflammatory condition that is associated with airway hyper-responsiveness and partially reversible airway obstruction [1]. The inflammatory process of asthma has traditionally been considered to mainly occur in the large airways [2]. Accumulating evidence, including surgically resected lung tissue [3–5], autopsy lung specimens [6–8] and transbronchial biopsies [9,10], indicates that the chronic inflammation is irregularly distributed throughout the airways, especially the small airways and the parenchyma [3]. The small airways are those bronchial passages that are less than 2 mm in diameter, and they comprise approximately 80%

of the total surface area in the lung [11]. The small airways supply only 10% of the total airway resistance in normal subjects [12], but they supply seven-fold more resistance in mild asthma patients [13]. In comparison with the large airways, the small airways cause major airflow restriction, inflammatory cell infiltration (especially by T cells and eosinophils) [3,4] and structural remodeling [14,15]. Therefore, small-airway abnormalities consist of small-airway inflammation, airflow obstruction and structural remodeling [16,17]. To date, many parameters have been used to assess the small airways, including functional parameters, biomarkers and imaging [16–19]. However, there is still no gold standard for evaluating the small airways. The pulmonary function test is non-invasive, economical and simple and is considered by a number of people to be the most popular method to detect small-airway abnormalities. A forced expiratory flow between 25% and 75% of the forced vital capacity (FEF_{25-75%}) and residual volume (RV) have been used to measure air-trapping in the

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small airways. However, measurement of the FEF25–75% and RV may be affected by the forced vital capacity and total lung capacity [20]. Impulse oscillometry (IOS) uses a regular square wave on the airway to measure the resistance during the patient's tidal breathing. This technology, which is used for detecting small airways, includes the parameters of peripheral airway resistance (R5–R20) and reactance area (XA). R5–R20 equals the difference between R5, reflecting the total airway resistance, and R20, reflecting the proximal airway resistance [21,22]. The single-breath nitrogen (sbN2) washout test has been used to detect ventilation inhomogeneity (phase III slope) and closure (closing volume, closing capacity) of the small airways [23]. The multiple-breath nitrogen washout (MBW) test has been used to distinguish ventilation heterogeneity based on the two parameters Scond (conductive ventilation heterogeneity) and Sacin (acinar ventilation heterogeneity) [24]. However, the influences of poor reproducibility and aging need to be considered in the nitrogen washout tests [24]. Transbronchial biopsies are used to directly measure the small airways or alveolar inflammation but cannot be widely performed, as these biopsies are invasive. Sequential sputum induction has been considered a relatively direct method for evaluating airway inflammation. The eosinophil cationic protein (ECP) levels or the number of eosinophils in the late-phase induced sputum are related to small-airway inflammation [25]. Unfortunately, the precise anatomical compartment from which induced sputum samples originate is not clearly defined. Measuring the fractional exhaled nitric oxide (FeNO) is a non-invasive means of detecting airway inflammation that is performed to distinguish nitric oxide originating from the conducting airways from nitric oxide from the pulmonary alveolus (CANO) by monitoring the expiratory flow [26]. However, this technology requires computational extrapolation. Regional air-trapping and the airway wall thickness are used to assess the small airways by high-resolution computed tomography (HRCT). Higher lung attenuation indicates less air-trapping [27], and the epithelial reticular basement membrane indicates the airway wall thickness [28]. Therefore, HRCT is considered to be a valuable tool for assessing small-airway closure and remodeling. However, costs and radiation hamper the development of this technology. At present, inhaled corticosteroids (ICSs) are still well established as the first-line treatment in current asthma management guidelines [1]. Many studies have already proven that ICSs can alleviate airway inflammation and improve lung function in asthma patients. However, conventional ICSs, which produce particle sizes in the range of approximately 3 μm [29], may not reach all parts of the bronchial trees [30]. Therefore, it is uncertain whether ICSs have an effect on the small airways.

Description of the interventions

Another type of medicine for asthma therapy is leukotriene receptor antagonists (LTRAs). There are three different commercially available and widely accepted leukotriene receptor antagonists (LTRAs), each with specific dosing regimens: (a) Montelukast (Singulair[®], Merck, Whitehouse Station, New Jersey, USA), 4 mg for ages 2 to 5 years old, 5 mg for ages 6 to 14 years old and 10 mg for ages greater than 15

years old, once daily at bedtime; (b) Zafirlukast (Accolate[®], AstraZeneca, Wilmington, Delaware, USA) 10 mg for ages 5 to 12 years old and 20 mg for ages greater than 12 years old, twice daily; and (c) Pranlukast (Onon[®], Ono Pharmaceuticals, Osaka, Japan) 450 mg for adults, once daily [31].

How the interventions might work

Leukotrienes, which are mainly derived from mast cells and eosinophils, cause bronchoconstriction, airway smooth muscle proliferation, inflammatory cell infiltration, microvascular permeability, neuronal input interactions and mucus secretion [31]. Leukotrienes play an important role in the pathogenesis of airway remodeling. Extracellular matrix remodeling mainly occurs in the outer area of the small airways [15]. The remodeling process thickens the airway wall by increasing the number of fibroblasts and the amount of extracellular matrix [15,32]. LTRAs can arrive at the small airways and selectively antagonize the leukotriene receptor, which is located on the plasma membranes of smooth muscle cells [33]. Henderson et al found that LTRAs could block infiltration by eosinophils and airway mucus release in an ovalbumin (OVA)-treated mouse asthma model [34]. Subsequently, the researchers also reported that LTRAs prevent fibrosis/subepithelial collagen deposition [35], even reversing this fibrotic process in the OVA-treated mouse asthma model [36]. In clinical trials, some evidence indicates that LTRAs can reduce bronchial hyper-responsiveness [37] and that they have clinical safety and tolerability profiles comparable to placebo [38]. In addition, adding LTRAs to ICSs is more efficacious than using ICSs alone for improving the clinical symptoms of asthmatics [39,40]. However, these outcomes, which tend to focus on symptom control and lung function in the large airways, may not adequately evaluate small-airway abnormalities. Subsequently, Zeidler et al. [41] began to study the effects of LTRAs on small-airway abnormalities using different detection methods. Therefore, it was necessary for us to do a systematic review and meta-analysis.

Methods

Search strategy

We searched the databases of the Cochrane Central Register of Controlled Trials (The Cochrane Library 2012, Issue 12), MEDLINE (1946 to December 2012), and EMBASE (1974 to December 2012). All of the records were searched using the following terms: (asthma*) AND (leukotriene antagonist* OR leukotriene receptor antagonist* OR LTRA* OR montelukast OR pranlukast OR zafirlukast) AND (small airway* OR peripheral airway* OR distal airway* OR alveolar*) AND [(random* OR controlled OR trial OR randomized controlled trial (RCT))]. The abstract books of the American Thoracic Society and European Respiratory Society were also searched by hand.

Inclusion criteria

We included RCTs if the following criteria applied: (a) they were designed by parallel or crossover groups without language restrictions; (b) they defined the diagnostic criteria of asthma using the Global Strategy for Asthma

Management and Prevention [1]; (c) they included participants in whom small-airway abnormalities had been detected without age or gender limitations; (d) they made the following main comparisons: LTRAs versus placebo, LTRAs versus ICSs, or LTRAs plus conventional treatment versus conventional treatment alone; (e) the interventions had been administered for at least 4 weeks; and (f) oral steroids and inhaled short-acting β_2 -agonists were allowed as rescue interventions.

Exclusion criteria

Studies were excluded if the following criteria applied: (a) the participants had a respiratory infection within 2 weeks; (b) the participants had received a treatment with LTRAs within 2 weeks; (c) the participants had chronic obstructive pulmonary disease or other respiratory diseases; and (d) the participants had a long history of smoking.

Assessment of risk of bias in included studies

Two reviewers independently assessed the quality of each study according to the Cochrane Handbook [42]. Inconsistencies were discussed with a third reviewer to obtain consensus. Additional methods information was included in an online depository (Supplementary Material).

Statistical methods

The RevMan software 5.1 (Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration) was used for the meta-analysis. Because the outcome data were continuous variables, the data were extracted using the pooled mean difference (MD) or standardized mean difference (SMD) with a 95% confidence interval (CI). Testing for heterogeneity was performed using a standard χ^2 test with a significance level of $\alpha = 0.1$, and the I^2 statistic was used to quantify heterogeneity. A result with $p > 0.1$ and $I^2 < 50\%$ indicated that the level of heterogeneity was acceptable. Thus, we chose the fixed-effect model for the meta-analysis. For a result with $p < 0.1$ or $I^2 > 50\%$, we had to explain the reasons for the heterogeneity, including clinical heterogeneity, methodological heterogeneity and statistical heterogeneity. We assessed the overall quality of the evidence for each comparison using the GRADE approach and the GRADE-profiler software 3.6 [43]. The quality of the evidence was based on the following five factors: study limitations, inconsistency, indirectness, imprecision and publication bias. There were four grades of evidence from “high quality” to “very low quality” [43].

Results

Study selection

A total of 145 articles were searched and managed using Endnote X5 software (Stamford, The USA: Thomson Corporation). After identification through the titles and abstracts, 34 articles were excluded because they were duplicate references, 20 were excluded because they were not RCTs, 4 were excluded because the subjects were non-asthmatics or had respiratory complications, 4 were excluded because the interventions were not LTRAs, 2 were excluded because the subjects were not humans and

62 were excluded because the outcomes were not related to small-airway abnormalities. After reviewing the full text of the remaining articles, 10 articles were excluded because the outcomes were not related to small-airway abnormalities, and 1 was excluded because the comparison groups did not meet the inclusion criteria. Ultimately, 8 RCTs [41,44–49] were included in our study. However, only 5 RCTs [41,46–48,49] were included in the meta-analysis because of insufficient data [44,45] or skewed data distributions in the other 3 studies [22]. The study flow diagram is shown in Figure 1.

Description of the included studies

Four RCTs [44–47] used a parallel-group design, and 4 RCTs [41,48,49] used a crossover design. One RCT [44] was a conference paper. Children and adults were all enrolled in our study at similar sex ratios. The asthma severity ranged from mild to moderate. The administration time ranged from 4 to 48 weeks. In the comparison groups, 4 RCTs [41,46–48] compared LTRAs with placebo, 2 RCTs [45,47] compared LTRAs with ICSs, and 4 RCTs [22,44,47,49] compared LTRAs plus conventional treatment with conventional treatment alone. The outcome was improvement in small-airway abnormalities, which was assessed using various biological, functional and imaging parameters. The parameters included lung attenuation and airway wall thickness [41,44], FEF25–75% [41,45–47,49], RV [41,46,48], ECP levels or the number of eosinophils in sequential sputum inductions [22], R5–R20 [22], XA [22] and CANO [49]. The characteristics of the included studies are shown in Table 1. The results of the included studies are shown in Tables 2–4.

Risk of bias assessment

All 8 of the RCTs [41,44–49] mentioned randomization. However, only 1 RCT [47] described the methods of randomization, and 1 RCT [22] described the process of allocation concealment. Double-blinding was mentioned in the methods of 4 RCTs [41,45,47,48]. One RCT [49] used an open-label design. Three RCTs [22,44,46] did not describe methods for blinding. Incomplete outcome data were reported in 6 RCTs [22,41,44–47], including loss to follow-up, and 1 RCT [41] reported a withdraw rate greater than 15%. All of the included RCTs [41,44–49] reported every outcome that was described in the methods. All of the included RCTs [41,44–49] declared that the data collection and analysis were not related to the pharmaceutical industry. The risk of bias in the included studies is shown in Table 5.

Meta-analysis

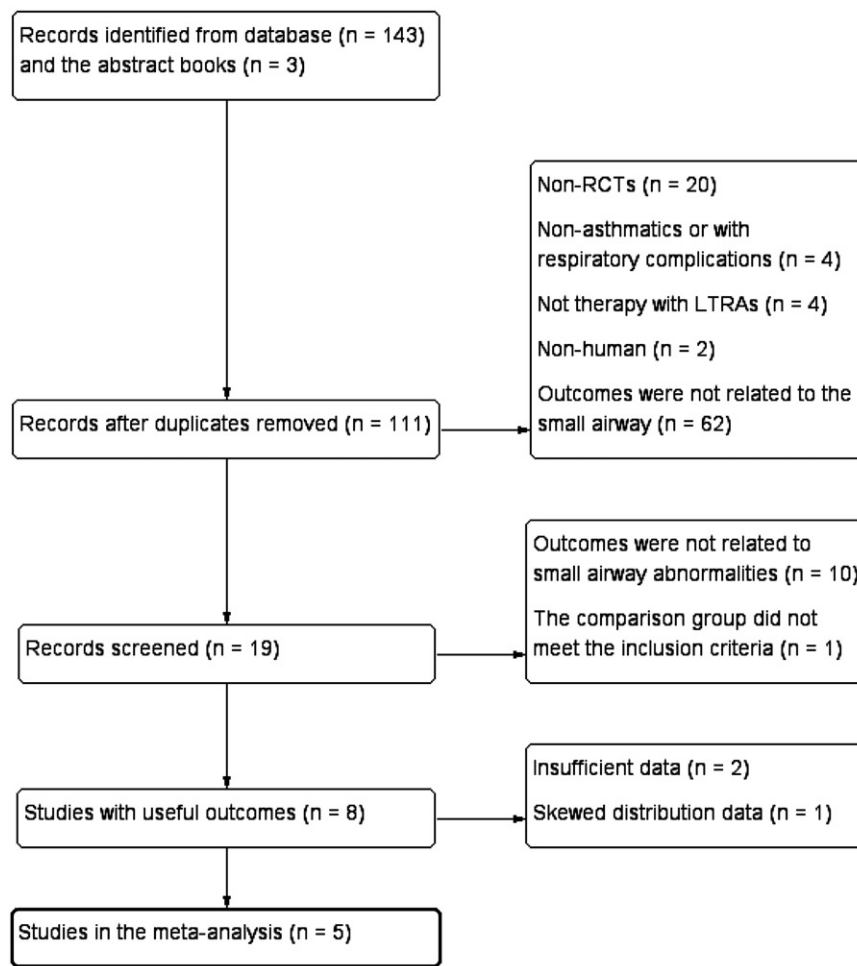
(1) LTRAs versus placebo

HRCT

One RCT (41) showed that an LTRA was more efficacious than placebo in reducing regional air-trapping on HRCT (MD 61.00; 95% CI, 26.32–95.68; $p < 0.001$).

FEF25–75%

Three RCTs [41,46,47] reported changes in FEF25–75% when comparing LTRAs with placebo. There was no heterogeneity among the 3 RCTs ($p = 0.40$, $I^2 = 0\%$). The pooled MD for the treatment effect was 5.29 (95% CI, –4.05 to



14.62; $p = 0.27$), showing no improvement in the FEF25–75% in participants receiving LTR compared with patients receiving placebo (Figure 2).

RV

Three RCTs [41,46,48] reported changes in RV when comparing LTRAs with placebo. One RCT [48] showed its result for the parameter of residual volume as the percent predicted (RV% predicted), while other RCTs [41,46] displayed their results as the ratio of the residual volume to the total lung capacity (RV/TLC). Therefore, the SMD was used as a summary statistic. There was no heterogeneity among the 3 RCTs ($p = 0.58$, $I^2 = 0\%$). The pooled SMD for the treatment effect was -0.85 (95% CI, -1.29 to -0.42 ; $p < 0.001$), showing a reduction in RV in participants receiving LTRAs compared with patients receiving placebo (Figure 3).

(1) LTRAs versus ICSs

FEF25–75%

There was only 1 RCT [47] included in the meta-analysis that showed no significant difference in the FEF25–75% between LTRAs and ICSs (MD, 4.00; 95% CI, -14.79 to 22.79 ; $p = 0.68$). However, Larsen et al [45] showed an improvement (MD, 1.147; 95% CI, 0.819 to 1.475; $p < 0.001$) in the FEF25–75% when comparing ICSs with LTRAs over the first 12 weeks of treatment. However, there was no significant difference (MD, 0.002; 95% CI, -0.180 to 0.185 ; $p = 0.980$) between the treatments from 12 to 48 weeks.

XA

Larsen et al. [45] showed no significant difference (MD, -0.209 ; 95% CI, -1.116 to 0.699 ; $p = 0.652$) in XA when comparing ICSs with LTRAs over the first 12 weeks of treatment. However, there was an improvement (MD, -0.567 ; 95% CI, -1.073 to -0.062 ; $p = 0.028$) for ICSs compared with LTRAs from 12 to 48 weeks.

(1) LTRAs plus conventional treatment versus conventional treatment alone

FEF25–75%

Two RCTs [47,49] reported changes in the FEF25–75% when comparing LTRAs plus conventional treatment with conventional treatment alone. There was no heterogeneity between the 2 RCTs ($p = 0.67$, $I^2 = 0\%$). The pooled MD for the treatment effect was 2.67 (95% CI, -10.83 to 16.16 ; $p = 0.70$), showing no significant difference in FEF25–75% between the two groups (Figure 4).

However, 3 RCTs [22,44,49] reported improvement in small airway parameters on HRCT ($p < 0.05$), CANO ($p = 0.04$), R5–R20 ($p = 0.032$), XA ($p = 0.014$), ECP levels ($p = 0.045$) and the number of eosinophils in late-phase sputum ($p = 0.035$) when comparing LTRAs plus conventional treatment with conventional treatment alone.

Quality of the evidence

The quality of the evidence was based on the following five factors. (a) Study limitations: Because the methods of random

Table 1. Characteristics of included studies.

Study ID	Study design	Parameters	Number	Age (years)	Gender	Asthma severity	Administration time (weeks)	Drop outs
Havlicu [44]	Parallel group	HRCT	IG ₂ : 19 CG ₃ : 19	Undescribed	Undescribed	Mild to moderate	8	Undescribed
Kraft [48]	Crossover	RV	19	38.1 ± 3.2	Male (6) Female (13)	Mild	4	Undescribed
Larsen [45]	Parallel group	FEF25%–75%, XA	IG ₁ : 95 CG ₂ : 95 CG ₃ : 95	6 to 14	Undescribed	Mild to moderate	48	3%
Ohbayashi [22]	Crossover	XA, R5-R20, Eosinophils cationic protein levels or eosinophils in late phase sputum	31	61.1 ± 17.8	Male (15)	Moderate	4	1 (3.1%)
Spahn [46]	Parallel group	FEF25%–75%, RV	IG ₁ : 11 CG ₁ : 10	13.0 ± 0.5	Female (16) Male (11)	Mild to moderate	8	1 (9.1%)
Stelmach [47]	Parallel group	FEF25%–75%	IG ₁ : 29 IG ₂ : 29 CG ₁ : 27 CG ₂ : 29 CG ₃ : 29	6 to 18	Female (10) Male (105) Female (40)	Moderate	4	1 (10%) 0 0 2(6.9%) 0 0 0
Yasui [49]	Crossover	FEF25%–75%, CANO	25	24 to 86	Male (9) Female (16)	Mild to moderate	8	
Zeidler [41]	Crossover	HRCT, FEF25%–75%, RV	20	36.0 ± 13.5	Male (9) Female (7)	Mild to moderate	4	4 (20%)

CANO: Alveolar nitric oxide concentration, CG: Control group, CG₁: Placebo, CG₂: Inhaled corticosteroid, CG₃: Conventional treatment group, FEF25%–75%: Forced expiratory flow between 25% and 75% of forced vital capacity, HRCT: High resolution computed tomography, IG: Interventions group, IG₁: Leukotriene receptor antagonists, IG₂: Leukotriene receptor antagonists plus conventional treatment group, Mean ± standard deviation if available, RV: Residual volume, R5-R20: The fall in resistance from 5 to 20 hertz, XA: Reactance area.

Table 2. Results of included studies (Comparison of leukotriene receptor antagonists versus placebo).

Parameters	Study ID	Data presentation	Results
HRCT	Zeidler [41]	Difference in change from baseline	IG: 39 ± 48 CG: -22 ± 52
FEF25–75%	Spahn [46]	Difference after treatment	IG: before treatment 70.5 ± 5.3^a IG: after treatment 66.5 ± 4.9^a CG: before treatment 61.3 ± 4.9^a CG: after treatment 61.00 ± 7.2^a
			IG: before treatment 91.3 ± 6.8^a IG: after treatment 97.8 ± 5.2^a CG: before treatment 98.5 ± 6.5^a CG: after treatment 90.6 ± 7.8^a
	Stelmach [47]	Difference after treatment	IG: 6.8 ± 16.8 CG: 0.2 ± 21.0
	Zeidler [41]	Difference in change from baseline	IG: before treatment 179.2 ± 14.0^a IG: after treatment 147.1 ± 10.3^a CG: before treatment 178.2 ± 7.0^a CG: after treatment 188.1 ± 10.8^a
RV	Spahn [46]	Difference after treatment	IG: -18.68 ± 8.41 CG: before treatment 162.05 ± 11.60 CG: after treatment 149.35 ± 7.78
			IG: -44.9 ± 44.4 CG: -3.6 ± 28.1
	Kraft [48]	Difference in change from baseline	
	Zeidler [41]	Difference in change from baseline	

CG: Control group, FEF25%–75%: Forced expiratory flow between 25% and 75% of forced vital capacity, HRCT: High resolution computed tomography, IG: Interventions group, Mean $\pm$ standard deviation if available, RV: Residual volume.

^a:Mean $\pm$ standard error.

Table 3. Results of included studies (Comparison of leukotriene receptor antagonists versus inhaled corticosteroid).

Parameters	Study ID	Data presentation	Results
FEF25–75%	Larsen [45]	Difference between groups	-1.147 (95% CI 0.819 to 1.475), treatment of 12 weeks -0.002 (95% CI -0.180 to 0.185), treatment of 48 weeks
			IG: before treatment 91.3 ± 6.8^a IG: after treatment 97.8 ± 5.2^a CG: before treatment 90.4 ± 6.9^a CG: after treatment 92.9 ± 5.4^a
	Stelmach [47]	Difference after treatment	
XA	Larsen [45]	Difference between groups	0.209 (95% CI -1.116 to 0.699), treatment of 12 weeks 0.567 (95% CI -1.073 to -0.062), treatment of 48 weeks

CG: Control group, CI: Confidence interval, FEF25%–75%: Forced expiratory flow between 25% and 75% of forced vital capacity, IG: Interventions group, Mean $\pm$ standard deviation if available, XA: Reactance area.

^a:Mean $\pm$ standard error.

sequence generation and allocation concealment were not clearly stated in some studies [41,46,47,49], we had to downgrade the quality of the evidence by 1 level. One study [49] used an open-label design. However, the outcome was an objective index, and the assessors were blinded during this study, so the bias should be limited. (b) Inconsistency: If the p value for heterogeneity was greater than 0.1 and the I^2 was 0%, then the quality of the study was not downgraded due to inconsistency. (c) Indirectness: No indirect comparisons were found in any of the included studies. (d) Imprecision: The total number of participants was less than 400 for each type of comparison. However, the measurements of the outcomes were based on objective parameters. Thus, we considered the results to be precise. (e) Publication bias: We considered all of the studies to be free of publication bias in the meta-analysis because they reported all of the outcomes that were described in the methods. No confounding factors that might change the effectiveness were found. In addition, there was no dose-response gradient. In general, the quality of evidence for each type of comparison in the meta-analysis was moderate.

Discussion

Summary of results

Research on the small airways is a highly active area. The aim of this study was to investigate the effects of LTRA treatment on parameters related to small-airway abnormalities in asthmatics. The main conclusions are that (a) compared with placebo, LTRAs improve the parameters related to small-airway abnormalities; (b) ICSs are more effective in this respect than LTRAs; and (c) a combination of LTRAs and conventional treatment is more effective than conventional treatment alone. The FEF25–75%, which has been used for the detection of small-airway obstruction, is theoretically effort-independent [50–52]. However, in this meta-analysis there is only very low-quality evidence to suggest an improvement in FEF25–75% in participants receiving LTRAs compared with patients receiving placebo. There was not even improvement in the FEF25–75% when comparing LTRAs with ICSs, nor when comparing LTRAs plus conventional treatment with conventional treatment alone. Nieto et al. [21] also reported that there was a decrease in the impulse oscillometry parameters but no significant

Table 4. Results of included studies (Comparison of leukotriene receptor antagonists plus conventional treatment group versus conventional treatment group).

Parameters	Study ID	Data presentation	Results
FEF25–75%	Stelmach [47]	Difference after treatment	IG: before treatment 90.4 ± 6.4^a IG: after treatment 98.2 ± 4.6^a CG: before treatment 98.5 ± 5.3^a CG: after treatment 96.5 ± 5.0^a
	Yasui [49]	Difference after treatment	IG: before treatment 48.4 ± 35.3 IG: after treatment 53.4 ± 33.9 CG: before treatment 43.8 ± 27.0 CG: after treatment 49.4 ± 35.4
HRCT	Havluca [44]	Difference in change from baseline	IG: undescribed CG: undescribed $p < 0.05$
CANO	Yasui [49]	Difference between groups	IG: before treatment 6.45, (4.23 to 10.70) ^b IG: after treatment 4.10, (2.30 to 6.60) ^b $p = 0.04$ CG: before treatment (undescribed) CG: after treatment (undescribed) P = insignificance
R5 - R20	Ohbayashi [22]	Difference between groups	IG: 0.050 (0.030–0.110) ^b CG: 0.500(0.030–0.073) ^b $p = 0.032$
XA	Ohbayashi [22]	Difference between groups	IG: 0.570(0.308–1.045) CG: 0.410 (0.263–0.820) $p = 0.014$
Eosinophils cationic protein levels in late phase sputum	Ohbayashi [22]	Difference between groups	IG: undescribed CG: undescribed $p = 0.045$
Eosinophils in late phase sputum	Ohbayashi [22]	Difference between groups	IG: $6.00 \pm 6.31\%^c$ CG: $9.96 \pm 7.46\%^c$ $p = 0.035$

CANO: Alveolar nitric oxide concentration, CG: Control group, FEF25–75%: Forced expiratory flow between 25% and 75% of forced vital capacity, HRCT: High resolution computed tomography, IG: Interventions group, Mean $\pm$ standard deviation if available, R5-R20: The fall in resistance from 5 to 20 hertz, XA: Reactance area.

^aMean $\pm$ standard error.

^bMedian (interquartile range).

^cThe mean percentages.

Table 5. Methodological characteristics of included studies.

Study ID	Randomization appropriate	Allocation concealed	Blinding of patients and personnel	Outcome assessor blinded	Incomplete outcome	Selective reporting	Conflict of interest
Havluca [44]	?	?	?	+	?	?	?
Kraft [48]	?	?	+	+	?	+	+
Larsen [45]	?	?	+	+	?	+	+
Ohbayashi [22]	?	+	?	+	+	+	+
Spahn [46]	?	?	?	+	+	+	+
Stelmach [47]	+	?	+	+	+	+	+
Yasui [49]	?	?	–	+	+	+	+
Zeidler [41]	?	?	+	+	–	+	+

+: Yes; –: No;?: Unclear.

improvement in the FEF25–75% in participants receiving montelukast compared with patients receiving no preventive treatment. Whether the FEF25–75% is an appropriate parameter for the detection of small-airway abnormalities remains unclear. The FEF25–75% is not only well correlated with bronchodilator responsiveness, but it is also used to predict reversible airflow obstruction [53,54]. However, the measurement of the FEF25–75% may be affected by the forced vital capacity [20,54]. In contrast, the FEF25–75% is poorly correlated with other lung function parameters such as the

RV/TLC [54]. In addition, the FEF25–75% can only be used to distinguish airflow obstruction when the airway resistance and forced expiratory volume in one second are normal [55,56].

In this study, there was no significant difference in the FEF25–75% for participants receiving LTRAs compared with participants receiving ICSs. Because parts of the ICSs dose may still reach the small airway. Some investigators have found that small-particle pressurized metered dose inhalers (PMDIs), such as hydrofluoroalkane (HFA)-beclomethasone

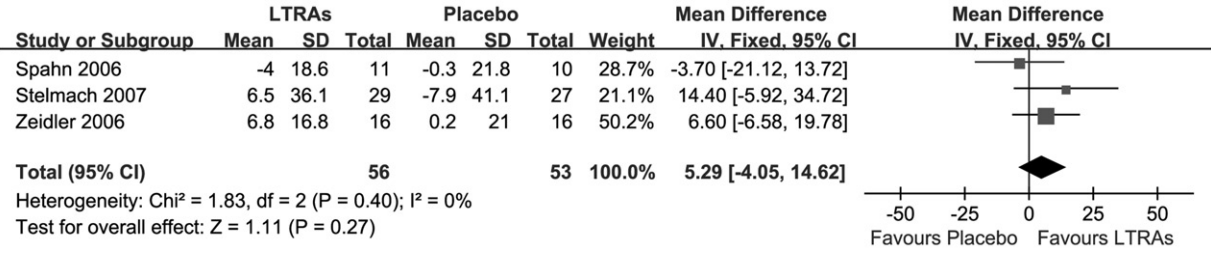


Figure 2. Pooled MD for the improvement of FEF25–75% of eligible studies comparing LTRAs with placebo (CI: Confidence interval, FEF25–75%: Forced expiratory flow between 25% and 75% of forced vital capacity, LTRAs: Leukotriene receptor antagonists, MD: Mean difference).

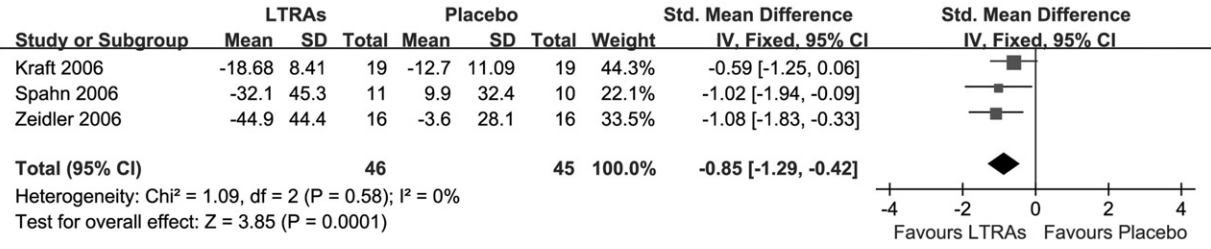


Figure 3. Pooled SMD for the improvement of RV of eligible studies comparing LTRAs with placebo (CI: Confidence interval, LTRAs: Leukotriene receptor antagonists, RV: Residual volume, SMD: Standardized mean difference).

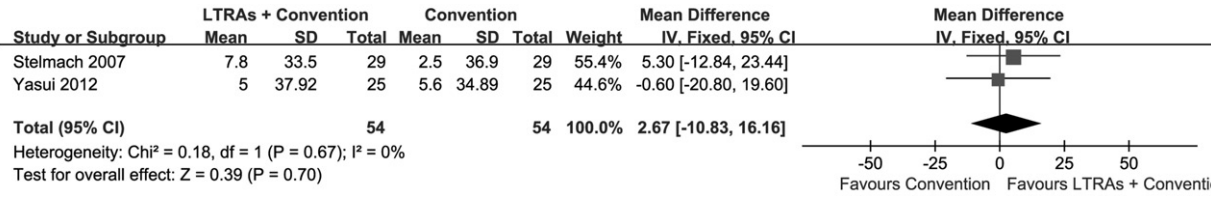


Figure 4. Pooled MD for the improvement of FEF25–75% comparing LTRAs plus conventional treatment with conventional treatment (CI: Confidence interval, FEF25–75%: Forced expiratory flow between 25% and 75% of forced vital capacity, LTRAs: Leukotriene receptor antagonists, MD: Mean difference).

and HFA-ciclesonide inhalers, with a particle size of approximately 1 μm, had a higher lung deposition than conventional inhalers [29,57]. Unfortunately, none of these RCTs was searched for the meta-analysis. Larsen et al. [45] reported no significant differences in the FEF25–75%, but they did report an improvement in the XA when comparing ICSs with LTRAs after 48 weeks of treatment. Impulse oscillometry seems more specific and sensitive than spirometry for the detection of pediatric asthma [58], so XA is sensitive to alterations in peripheral airflow obstruction [59,60].

In addition, the 3 included RCTs [22,44,49] suggested that LTRAs plus conventional treatment was more effective than conventional treatment alone for small-airway abnormalities in asthmatics. Fritscher et al. [61] also reported that there was a nearly significant decrease for CANO parameters in asthmatics receiving montelukast plus fluticasone ($p=0.08$) compared with patients receiving only fluticasone ($p=0.1$).

The integrity of the results and applicability of the evidence

At present, there is no gold standard for the measurement of small-airway abnormalities in asthmatics. In this review, results for conventional parameters were used to evaluate the effect on LTRAs in the treatment of the small-airway abnormalities. Hence, the integrity of the result was most

likely affected. In other words, no single parameter could fully reflect the effects of treatment. Therefore, we need a more comprehensive evaluation of the measured outcomes. Similarly, some studies [44,45,22] were only described in this review because of their insufficient original data or skewed data distributions. On that level, the integrity of the results was also affected.

Potential bias in the evaluation process

The potential sources of bias in the study were as follows: (a) Because some differences might exist in many aspects of the included articles such as diagnostic criteria, drug dose, formulation, clinical course, disease severity, detection methods and so on, the results might have been affected. (b) Because some results from specific studies lacked baseline data, we were unable to extract the data. These were studies ultimately not included in the meta-analysis, leading to publication bias. We could only describe the results because some studies have shown the results through skewed data distributions. (c) In this review, HRCT and other conventional parameters were used for comprehensive evaluation of the influence on LTRAs on small-airway abnormalities in asthmatics. However, there were still other parameters that were not included, such as closing volume in a single breath and inflammatory and remodeling markers in transbronchial

biopsy. (d) This review included only a small number of studies, which were mainly conducted in the US [41,45,46,48], with only 2 studies from Japan [22,49], and one each from Poland [47] and Turkey [44]. These small-sample studies do not yield many results and make it difficult to perform a meta-analysis incorporating a significant number of patients or studies. Thus, there is the potential for publication bias.

Conclusions

Despite such limitations, there is moderate-quality evidence to suggest that LTRAs may improve most of the conventional parameters for the detection of small-airway abnormalities in asthmatics. However, there is no evidence of the superiority of LTRAs over ICSs in improving the functional parameters related to small airways. Further, large-sample RCTs will be required to validate our results.

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Declaration of interest

None of the authors have a conflict of interest related to this work. The authors alone are responsible for the content and writing of this article.

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Assessment of risk of bias in included studies

We examined the following strategies (1) associated with low risk of bias (Yes), high risk of bias (No) or uncertain risk of bias (Unclear).

(1) Random sequence generation (selection bias): The methods of randomization included computer random number generator, random number table, envelopes, coin tossing, throwing dice, shuffling cards, drawing of lots and so on.

(2) Allocation concealment (selection bias): Participants or investigators could not be permitted to influence on interventions group before the eligible participants entered in the study.

Assessment of allocation concealment included central allocation, sequential numbers, non-transparent envelopes and so on.

(3) Blinding of participants and personnel (performance bias): Participants and investigators were blinded, and the blinding could not been broken easily.

(4) Blinding of outcome assessment (detection bias): Outcome assessors were blinded, or measured of outcome was based on objective parameters.

(5) Incomplete outcome data (attrition bias): The withdraw rate was assessed by the percentage of participants who lost to follow up. We considered the risk of attrition bias as “Yes” when the withdraw rate was less than 5%, as “No” when the withdraw rate was more than 5%. In another way, if the included studies specifically reported an intention to treat analysis, we considered it as “Yes”.

(6) Selective reporting (reporting bias): We assessed the reporting bias as “Yes” if the study reported all outcomes described in the methods.

(7) Other bias (the conflict of interest bias): We assessed the conflict of interest bias as “Yes” if the study declared that data collection was not related to the pharmaceutical factory.

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