Comparison of leukotriene receptor antagonists in addition to inhaled corticosteroid and inhaled corticosteroid alone in the treatment of adolescents and adults with bronchial asthma: a meta-analysis

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Summary

Background: **Leukotriene receptor antagonists (LTRA) have been recommended as treatment for persistent asthma. It is not clear whether oral LTRA in combination with inhaled corticosteroids (ICS) confers any additional benefit over ICS alone.**

Objective: **This meta-analysis was conducted to review the evidence for the benefits and risks of ICS-LTRA in comparison to ICS alone in bronchial asthma.**

Methods: **MEDLINE, EMBASE, LILACS, and CINAHL databases were searched for studies published through Aug 20, 2011. Studies comparing ICS-LTRA and ICS and those comparing ICS-LTRA and high-dose ICS were examined separately. Studies were pooled to yield odds ratios (ORs) or weighted mean differences (WMDs) with 95% confidence intervals (CIs).**

Results: Eight trials in which ICS-LTRA was compared with the same dose of ICS and five in which ICS-LTRA was compared with high-dose ICS were identified. In adults with mild to moderate asthma, the combination of ICS-LTRA improves the control of asthma when compared with same dose of ICS as monotherapy. The effects of ICS-LTRA therapy are similar to those of high-dose ICS in asthma control, but high-dose ICS is superior to ICS-LTRA with regard to improvement in some pulmonary function indices.

Conclusions: **In adults with mild to moderate asthma, though the effects were minimal, the combination of ICS-LTRA is recommended, when comparing its effects with the same dose ICS as monotherapy. The relative merits of ICS-LTRA and high-dose ICS therapy are uncertain and more research is needed.** ***(Asian Pac J Allergy Immunol 2012;30:130-8)***

Key words: *asthma, inhaled corticosteroid, leukotriene receptor antagonist, meta-analysis*

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Introduction

Bronchial asthma is a chronic airway inflammatory disorder in which many cells and cellular elements play important roles. The chronic inflammation is associated with airway hyper-responsiveness and variable airflow obstruction. Corticosteroids are currently the most effective anti-inflammatory medications and are considered as the first line treatment in persistent asthma.[1] In the majority of patients, mild to moderate asthmatic airway dysfunction is usually responsive to inhaled corticosteroids (ICS) and they form the mainstay of therapy. However, there is marked individual variability in responsiveness to ICS, with some patients requiring higher doses of ICS to achieve full therapeutic benefit. Because of the potential side effects of ICS, add-on therapy with another class of controller is preferable to increasing the dose of ICS in order to get clinical control.[1]

Among other anti-inflammatory medications, recent guidelines have recommended the use of leukotriene receptor antagonists (LTRA) in

persistent asthma.[1] Some meta-analyses comparing ICS and LTRA have been reported. In the systematic review by Ducharme,[2] the comparisons of LTRA versus placebo as add-on therapy to ICS, LTRA as add-on therapy to ICS versus double dose ICS, and LTRA versus placebo as add-on therapy to tapered doses of ICS in adult and children were analyzed. Their analysis revealed that ICS-LTRA (ICS plus LTRA) may modestly improve asthma control compared with ICS alone but this strategy cannot be recommended as a substitute for increasing the dose of inhaled glucocorticoids. Another systematic review by Joos et al.[3] in which conclusions were drawn from two well-designed trials[4,5] also showed a similar result, although only the only LTRA alalyzed was montelukast. Nowadays, there are other LTRA drugs, such as pranlukast, zafirlukast and zileuton, which are available for the treatment of asthma. More randomized controlled trials (RCTs) comparing LTRA as add-on therapy to ICS with ICS have been conducted since the previous reviews were carried out. In the light of all this new evidence, it is important that we analyze the efficacy and safety of ICS-LTRA as compared to different dosages of ICS.

The objective of this meta-analysis was to evaluate the benefits and risks of LTRA drugs as add-on therapy to ICS in asthmatic adolescents and adults compared with ICS monotherapy.

Methods

Data Sources and Searches

We searched MEDLINE, EMBASE, LILACS, and CINAHL databases for relevant articles published until Aug 20, 2011, with no lower date limit applied. The first MEDLINE search strategy retrieved citations containing the "leukotriene receptor antagonist OR montelukast OR pranlukast OR zafirlukast OR zileuton" and "inhaled corticosteroids OR budesonide OR beclomethasone OR fluticasone OR triamcinolone OR flunisolide" and "asthma" (Limits Activated: Randomized Controlled Trial, RCT). We modified these searches for the other databases. We screened reference lists from all retrieved articles and recent review articles to identify additional studies. There were no language restrictions. Results were double-checked and arbitrated by a second investigator.

Study Selection

We included full-text publications that presented original data from RCTs, and trials published solely in abstract form were excluded because methods and results could not be fully analyzed. Inclusion criteria for those trials included (1) patients aged older than 12 years with a clinical diagnosis of asthma before study entry; (2) RCTs (parallel group or crossover) without language restriction; (3) a minimum of 2 weeks of treatment with ICS compared with ICS-LTRA (the dose of ICS was maintained throughout the intervention period); and (4) the primary outcome variables were measures of pulmonary function, including changes from baseline in forced expiratory volume in the first second (FEV_1), percentage changes from baseline in FEV_1, changes from baseline in peak expiratory flow (PEF) which included morning and evening changes. The secondary outcome variables were measures of mean change from baseline in albuterol use, changes from baseline in symptom scores, percentage changes from baseline in eosinophil counts, and incidence of overall adverse effects.

Data Extraction and Quality Assessment

Two authors reviewed the titles and the abstracts, excluding irrelevant papers after each stage. Disagreements were resolved by discussion. The full texts of the remaining papers were searched and the following exclusion criteria applied: reviews, duplicated studies, those without relevant outcomes or those in which no quantitative results or p values were presented. We also contacted study authors for missing data. Included studies were assessed for methodological quality by using the Jadad Scale for Quality Assessment. A median score of 3 was used to distinguish moderate and high quality studies from poor quality studies.[6]

Statistical Analysis

Binary outcomes were pooled by using common relative risks (RRs) and 95% confidence intervals (CI). However, where studies reported no events occurring and thus contributed zero event rates to the analysis, we reported the risk differences, in addition to relative risk to incorporate their estimates in the analysis. The proportions of patients with severe exacerbations from each trial were pooled by using the fixed-effects method expressed as a Peto odds ratio (OR) with corresponding 95% CIs.

For quantitative and continuous data variables we calculated a fixed effect weighted mean difference (WMD) for data measured on the same scale. For data measured on different scales which could not be converted to a WMD, we pooled them using a fixed-effect standardized mean difference (SMD).

Table 1. Characteristics of trails included.

Study	Patients	Age range (mean)	Lung function FEV1% predicted	comparison	Study design	Duration of therapy (weeks)	comment
Laviolette 1999	393	15 ~ 78	50% ~ 85%	Mon 10mg/d + Bec 400μg/d Vs Placebo + Bud 400μg/d	Multicenter Double blind Randomized Parallel group	16	
Virchow 2000	368	17~71	Mild ~ moderate 49% ~ 79%	ZAF 160mg/d + Bec 1000μg/d vs Placebo+ Bec 1000μg/d	Multicenter Double blind Randomized Parallel group	6	Assessment made at 3 and 6 week We assessed the last results only
Dempsey, 2002	28	18~65	>70%	ZAF 40mg/d + Bec 400μg/d vs Placebo+ Bec 400μg/d	single blind Randomized crossover	2	
Vaquerizo 2003	639	18~70	≥50%	Mon 10mg/d + Bud 400~1600μg/d Vs Placebo + Bud 400~1600μg/d	Double blind Randomized Parallel group	16	
Price 2003	889	15~75	≥50%	Mon 10mg/d + Bud 800μg/d Vs Placebo + Bud 1600μg/d	Double blind Randomized	12	Some original data didn't offer
Riccioni 2003	39	(26)	60% ~ 85%	Mon 10mg/d + Bud 800μg/d Vs Placebo + Bud 1600μg/d Vs Placebo + Bud 800μg/d	Randomized Parallel group	12	
Sullivan 2003	28	19~50	>60%	Mon 10mg/d + FP 200μg/d Vs Placebo + FP 200μg/d	double blind Randomized crossover	8	
Cakmak 2004	21	16~48	>70%	ZAF 20mg/d + Bud 400μg/d vs Placebo+ Bec 400μg/d	Double blind Randomized Parallel group	6	
Perng 2004	49	18~77	Mild~ moderate	ZAF 20mg/d + Bud 400μg/d vs Placebo+ Bec 1200μg/d	Randomized	6	
Yildirim 2004	30	(36.93)	Moderate	Mon 10mg/d + Bud 400μg/d Vs Placebo + Bud 800μg/d	Randomized Parallel group	6	
Barnes 2007	75	15~70	>50%	Mon 10mg/d + Bud 800μg/d Vs Placebo + Bud 1600μg/d	Multicenter Double blind Randomized Parallel group	12	There were no difference of ECP, IL-8, days with asthma exacerbation % and quality of life mean between groups, and these original data couldn't be gotten
Djukanović 2010	103	(29.4)	>60%	Mon 10mg/d + FP 200μg/d Vs FP 200μg/d	Multicenter Double blind Randomized	12	

FEV1: forced expiratory volume in 1 second, ZAF: zafirlukast, Bec: beclomethasone, Mon: montelukast, Bud: budesonide, FP: fluticasone propionate

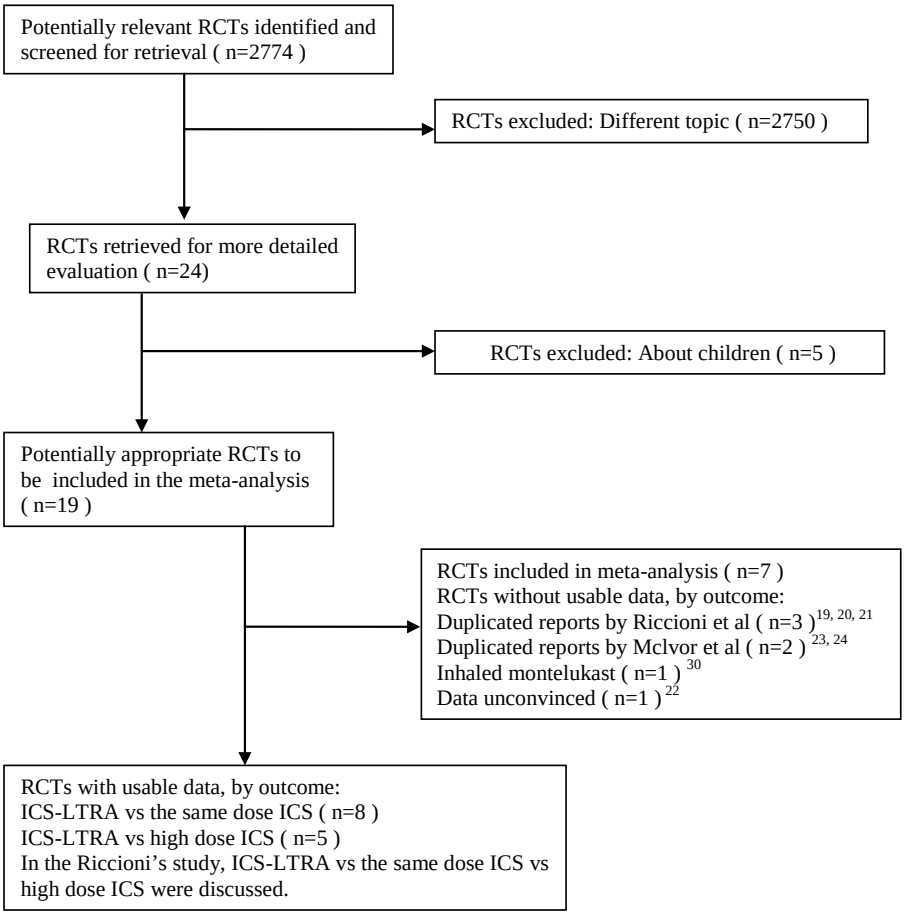

Figure 1. Flowchart for identification of studies. RCT, randomized controlled trial. ICS, inhaled corticosteroid. LTRA, leukotriene receptor antagonist.

Where possible, for each end point, we combined the results from individual studies to produce summary effect estimates. Heterogeneity was tested using the Breslow-Day test with a P value < 0.1 considered statistically significant. A random effects model was used if heterogeneity was found. The I^2 statistic was also calculated to efficiently test heterogeneity, with I^2<25%, 25-75%, and >75% considered to represent low, moderate, and high degree of inconsistency, respectively.[7] Publication bias was examined in funnel plots and tested with Egger's weighted regression method.[8]

All analyses were conducted using Cochrane Review Manage 5.0.23 (Cochrane Library Software, Oxford, United Kingdom).

Results

Overview of included studies (Table 1)

From an initial 2774 papers and abstracts identified from the literature searches, 12 trials met the selection criteria, 8 trials in which ICS-LTRA was compared to ICS[4-5,9-14] and 5 in which ICS-LTRA was compared to high-dose ICS were identified.[11,15-18] Among them, Riccioni et al.[11] studied both the comparison of ICS-LTRA vs ICS, and ICS-LTRA vs high-dose ICS. Some papers by Riccioni et al.[19-21] were excluded because of duplicated reporting. Huang et al.[22] trial was excluded, because the data in his results were not in accord with the data in the abstract. Some papers by McIvor et al.[23,24] were also excluded because of duplicated reporting and because data from adults and children in the trials were mixed and couldn't be distinguished. (Figure 1)

Methodological quality of the studies

Eight of the twelve trials (66.67%) were scored as being of moderate or high level (≥3) methodological quality. The median of the Jadad scores for the five trials comparing ICS-LTRA with high-dose ICS was 2.4. Only 2 of the 5 were scored as being of moderate or high level (≥3) methodological quality. The Jadad scores for the 12

trials ranged from 1 to 5, with a median of 3.25. (Table 2)

ICS-LTRA vs ICS

- **Changes from baseline in FEV_1 (L)**

Five hundred and fifty two patients from three trials[5,9,14] were considered for the analysis (271 treated with ICS-LTRA, 281 treated with ICS). ICS-LTRA was superior to ICS monotherapy in improving FEV_1 (mean difference 0.14 [95% CI 0.09 to 0.19] L, P<0.00001, I^2=52%).

- **Percentage changes from baseline in FEV_1 (%)**

One thousand two hundred and seventeen patients from five trials[4,5,11,12,14] were considered for this analysis (609 treated with ICS-LTRA, 608 treated with ICS). ICS-LTRA was superior to ICS monotherapy in improving FEV_1 in percentage (mean difference 2.83% [95% CI 1.16 to 4.5], P = 0.0009, I^2 = 26%). (Figure 2)

- **Changes from baseline in morning PEF (L/min)**

One thousand six hundred and fifteen patients from six trials[4,5,9,10,12,14] were considered for this analysis (805 treated with ICS-LTRA, 810 treated with ICS). ICS-LTRA was superior to ICS monotherapy in improving morning PEF (mean difference 8.81 [95% CI 4.70 to 12.92] L/min, I^2 = 0%, P < 0.0001,). (Figure 3)

- **Changes from baseline in evening PEF (L/min)**

Nine hundred and seventy six patients from five trials[5,9,10,12,14] were considered for this analysis (479 treated with ICS-LTRA, 497 treated with ICS). ICS-LTRA was superior to ICS monotherapy in improving evening PEF (mean difference 6.34 [95% CI 1.94 to 10.73] L/min, P = 0.005, I^2 = 1%). (Figure 4)

- **Decrease in β-agonist use**

One thousand one hundred and twenty one patients from 3 trials[4,5,14] were considered for this analysis (560 treated with ICS-LTRA, 561 treated with ICS). The efficacy of ICS-LTRA was similar to that of ICS monotherapy in decreasing the percentage of total daily β-agonist use (mean difference -0.40 [95% CI -1.6 to -0.8]%, P = 0.51, I^2 = 46%). However, Vaquerizo et al.[4] reported that patients treated by ICS plus montelukast had a greater decrease in rescue β-agonist use percentage (%) than those treated by ICS monotherapy. Virchow et al.[10] reported that patients treated by ICS plus zafirlukast showed a greater decline in rescue β-agonist use (puffs/day) than those treated by ICS monotherapy. Dempsey et al.[9] also reported that the patients treated by ICS plus zafirlukast had fewer rescue β-agonist use (puffs/12h day or night) than those treated by ICS monotherapy.

- **Changes from baseline in symptom scores**

Four trials[4,5,9,10] were included this index, but they used very different scales. A scale of 0-6 was used by Laviolette et al.[5] and Vaquerizo et al.[4] One thousand and thirty two patients from these studies were considered for this analysis (519 treated with ICS-LTRA, 513 treated with ICS). ICS-LTRA was superior to ICS monotherapy in decreasing asthma symptom scores (mean difference -0.11 [95% CI -0.20 to -0.01], P = 0.03, I^2 = 0%). Meanwhile, a scale of 0-3 was used by Virchow et al.[10] and a scale of 0-4 was used by Dempsey et al.[9] They both found that the decrease of symptom scores in the ICS-LTRA group was more than those in the ICS group.

Table 2. Quality of trails included, scoring by Jadad's method.

Study	Randomization/ allocation concealment appropriate	Blinding *	Dropouts reason	Quality domain
Laviolette 1999	2	2	1	5
Virchow 2000	2	2	1	5
Dempsey 2002	0	1	1	2
Vaquerizo 2003	2	2	1	5
Price 2003	1	2	1	4
Riccioni 2003	1	0	0	1
Sullivan 2003	1	2	0	3
Cakmak 2004	1	2	0	3
Perng 2004	1	0	0	1
Yildirim 2004	1	0	0	1
Barnes 2007	2	2	1	5
Djukanović 2010	2	2	1	5

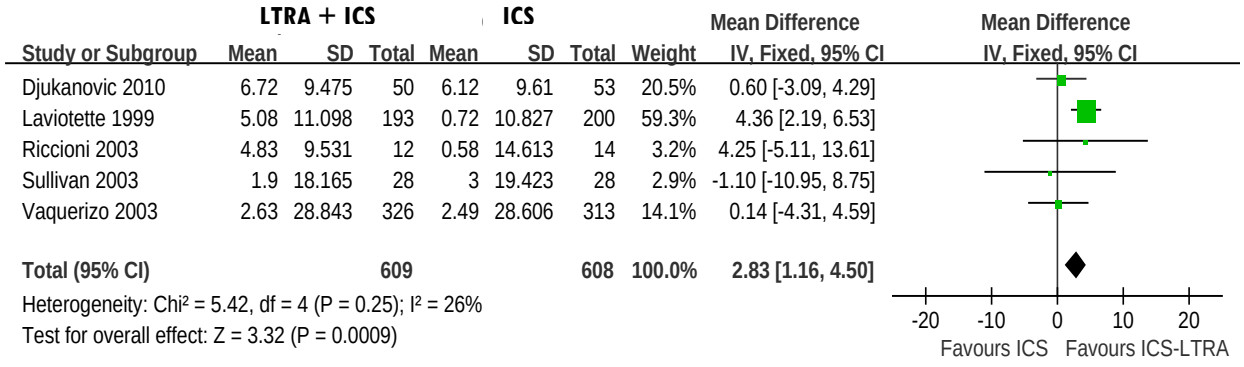

Figure 2. Summary effects on changes from baseline in FEV_1% comparing inhaled corticosteroids plus leukotriene receptor antagonists with same dose inhaled corticosteroids.
FEV1: forced expiratory volume in 1 second.

- **Adverse events**

One thousand four hundred and twenty one patients from 4 studies[4,5,10,13] were considered for this analysis (710 treated with ICS-LTRA, 711 treated with ICS). ICS-LTRA was similar to ICS therapy with regard to the incidence of adverse events (OR: 0.90 [95% CI: 0.58 to 1.39], *P*=0.64, I^2 = 50%). The commonly reported adverse events included influenza and headache. Forty-nine patients from 3 studies[4,5,10] were reported to have ceased their treatment because of serious adverse events and there was also no difference in the incidence of this between the two therapies (OR: 0.65 [95% CI: 0.36 to 1.19], *P*=0.17, I^2 = 0%).

ICS-LTRA vs high-dose ICS

- **Changes from baseline in FEV_1 % predicted (%)**

Fifty five patients from two studies[11,17] were considered for this analysis (27 treated with ICS-LTRA, 28 treated with high-dose ICS). There was no significant difference between ICS-LTRA and high-dose ICS therapy in improving FEV1 % predicted (mean difference 1.07 [95% CI -2.67 to 4.80] %, *P* = 0.58, I^2 = 0%).

- **Changes from baseline in PEF (L/min)**

Seventy nine patients from two studies[15,17] were considered for this analysis (43 treated with ICS-LTRA, 36 treated with high-dose ICS). ICS-LTRA therapy was less effective than high-dose ICS therapy in improving PEF (mean difference -19.64 [95% CI -38.06 to -1.22] L/min, *P* = 0.04, I^2 = 0%).

- **Percentage changes from baseline in PEF (%)**

Fifty five patients from two studies[11,17] were considered for this analysis (27 treated with ICS-LTRA, 28 treated with high-dose ICS). ICS-LTRA therapy was less effective than high-dose ICS therapy in improving PEF% (mean difference -5.01 [95% CI -8.35 to -1.68] %, *P* = 0.003, I^2 = 0%).

- **Percentage changes from baseline in eosinophil (%)**

Nine hundred and nineteen patients (463 treated with ICS-LTRA, 456 treated with high-dose ICS) from two studies[16,17] were considered for the analysis of peripheral blood eosinophilia. 74 patients (40 treated with ICS-LTRA, 34 treated with high-dose ICS) from two studies[11,15] were considered for the analysis of eosinophilia in induced sputum. All the reports concluded that the changes in peripheral blood eosinophilia and induced- sputum eosinophilia did not differ between the two groups, although meta analysis could not be carried out due to the absence of original data.

- **Decrease in β-agonist use (puffs/days)**

Seventy nine patients from two studies[15,17] were considered for this analysis (43 treated with ICS-LTRA, 36 treated with high-dose ICS). ICS-LTRA therapy more obviously decreased the daily use of β-agonist compared with high-dose ICS therapy (mean difference -0.21 [95% CI -0.03 to -0.09] puffs/day, *P* = 0.0004, I^2 = 0%). However, Price et al.[16] reported that there was no difference in the use of β-agonist between the two therapy methods, but their original data were not available for analysis.

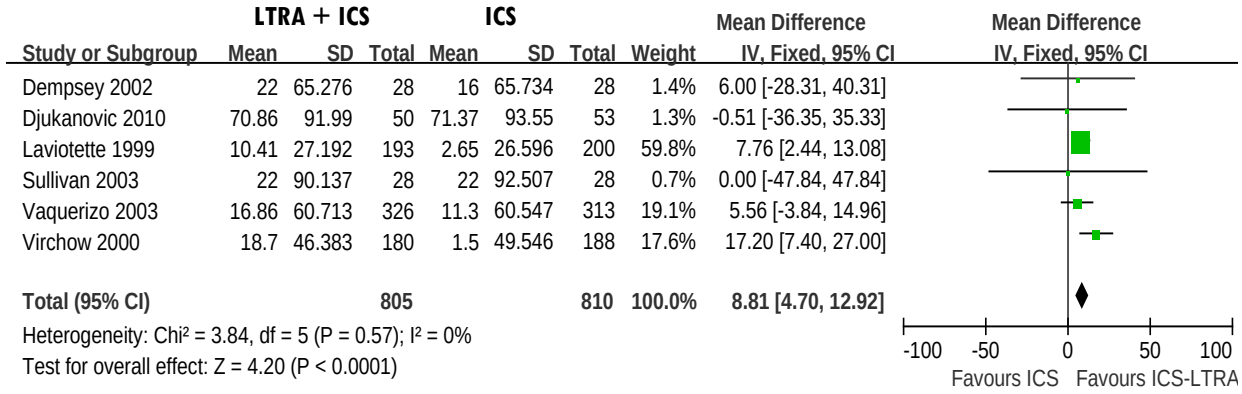

Figure 3. Summary effects on changes from baseline in morning PEF comparing inhaled corticosteroids plus leukotriene receptor antagonists with same dose inhaled corticosteroids PEF: peak expiratory flow.

- **Symptom score change**

Two trials,[15,18] which assessed symptom score change by the same methods, revealed that there was no difference of asthma symptom score change between the LTRA-ICS therapy and the ICS (double to triple dose) therapy. However, Barnes et al.[18] trial did not provide us with the original data and meta analysis could therefore not be done. Meanwhile, two other trials[16,17] also reported that no difference was found in the asthmatic symptom score change between the two therapy methods. Meta analysis was not done because the methods for measuring symptom scores were different.

- **Adverse events**

Nine hundred and ninety four patients from three studies[16-18] were considered for this analysis. ICS-LTRA was similar to high-dose ICS therapy with regard to the incidence of adverse events (OR: 0.82 [95% CI: 0.63 to 1.07], P=0.15, I^2 = 0%). The common adverse events were upper respiratory infection, worsening of asthma, headache and nausea. Neither of them reported serious adverse events.

Discussion

In asthmatic patients, leukotrienes play an important role in mediating bronchoconstriction and allergic airway inflammation.[25] Many previous studies have shown that leukotriene modifiers attenuate both early and late allergen responses and have anti-inflammatory effects. In current international or national guidelines, such as Global Initiative for Asthma guidelines, LTRA is also considered to be suitable for treatment of mild to moderate asthmatic patients, especially those who have less compliance with inhalation equipment.[1] Some systematic reviews and meta-analyses have shown that in mild to moderate asthmatic patients, ICS is superior to LTRA as controller monotherapy in improving pulmonary function, symptom and life quality, reducing the incidence of asthma exacerbations, and was similar to LTRA in the incidence of adverse events.[26-29] In this study, we aimed to analyse whether the treatment of ICS-LTRA was superior to ICS monotherapy in asthma patients.

Joos et al.[3] reported that montelukast as add-on therapy to ICS improves the control of mild to moderate asthma as compared with ICS monotherapy. To our knowledge, other LTRA drugs, such as zafirlukast, have not been compared in previous meta-analyses. In our study, the effects of montelukast and zafirlukast were both analyzed. We found that ICS-LTRA was superior to ICS in the improvement of FEV_1, FEV_1%, PEF morning and evening change, and decrease of asthma symptom scores, except decrease in β-agonist use, and that there was no significant difference in the risks of adverse events. Here, data from two studies[4,5] were used for the analysis of the decrease in β-agonist use and no significant difference was found between the two groups. This might be due to the great diversity of lung function and β-agonist need in the patients from the trial of Laviolette et al.[5] Another two studies also reported that ICS-LTRA decreased the need for β-agonist more than ICS.[9-10] Meta analysis could not be carried out due to the absence of same standard for β-agonist use assessment. Some trials discussed the change in eosinophils,[9,12] ICAM and E-selectin,[9] which are associated with airway inflammation, and found more obvious changes in the ICS-LTRA group when compared with the ICS group. Thus, we concluded that ICS-LTRA was

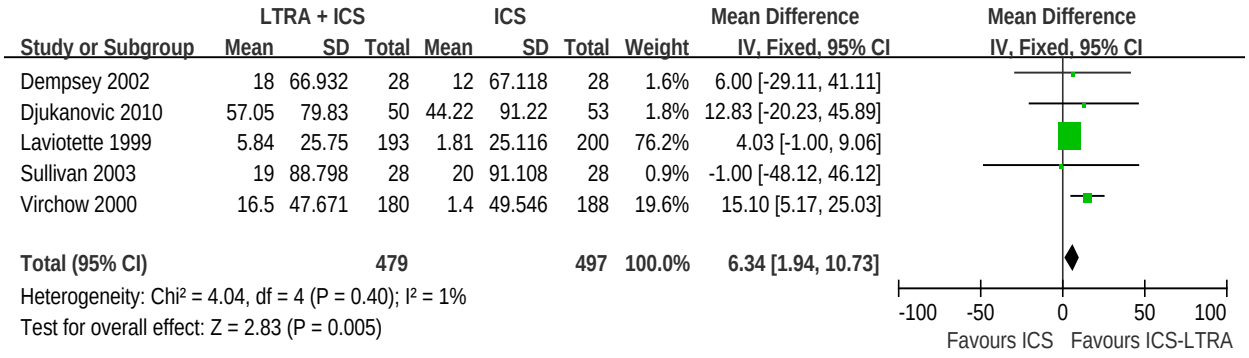

Figure 4. Summary effects on changes from baseline in evening PEF comparing inhaled corticosteroids plus leukotriene receptor antagonists with same dose inhaled corticosteroids PEF: peak expiratory flow.

superior to ICS monotherapy in asthma control. However, we should note that the total improvement is small, though there are significant differences between the the two therapeutic approaches.

Since ICS-LTRA was superior, we further assessed whether LTRA could be used as replacement therapy if the dose of ICS was being decreased. In this study, we found that the treatment of high-dose ICS was superior to ICS-LTRA in the improvement of PEF and PEF%, although a similar treatment effect in improvement of FEV1% was found in both of them. A more obvious decrease in β-agonist need was observed in the ICS-LTRA group compared with high-dose ICS group. However, there was no difference between the two therapies in β-agonist need in another large sample trial[16]. Thus, we still can not confirm whether ICS-LTRA therapy is superior to high-dose ICS therapy in relation to β-agonist need. We also found that there was no difference in asthma symptom score change between the ICS-LTRA therapy and the ICS (double to triple dose) therapy. A similar rate of adverse events was found between the two therapies. We therefore draw the conclusion that high-dose ICS is superior to ICS-LTRA with regard to improvement in some pulmonary function indices. We couldn't draw any conclusion from the above data as to which therapy is superior in asthma control and this might be due to lack of detailed information in the trials or the diversity in the patients included, which was too great to be ignored.

Most trials except 4 included in this meta-analysis were of good quality, and combined with homogeneous clinical characteristics of the studied samples. However, only 2 trials about high-dose ICS were of good quality. Concerning publication bias, funnel plots for the primary endpoints showed no clear evidence of publication bias and the test using Egger's method did not suggest publication bias for those dichotomous data. We also avoided selection bias by a systematic search and independent evaluation of trial inclusion by two reviewers. Most outcome measures across the trials were statistical homogeneous.

In conclusion, this meta-analysis suggests that ICS-LTRA is superior to ICS monotherapy in mild to moderate asthma control and there is no difference in the incidence in adverse events. The effects of ICS-LTRA therapy are similar to those of high-dose ICS in asthma control, but high-dose ICS is superior to ICS-LTRA with regard to the improvement in some pulmonary function indices. Because of the limitations of this meta-analysis, we recommend future work on the comparison of ICS-LTRA to high-dose ICS in the form of larger, longer, multicentre, double blind, randomized controlled trials to assess the validity of efficacy and the safety of such therapy.

Acknowledgements

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