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Leukotriene receptor antagonists do not improve lung function decline in COPD: a meta-analysis

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Abstract. – OBJECTIVE: Leukotriene receptor antagonists (LTRA), the anti-inflammatory agents, have been reported new therapeutic value in chronic obstructive pulmonary disease (COPD). However, the effects of LTRA on lung function decline in COPD were determined with inconsistent results and a meta-analysis is needed.

MATERIALS AND METHODS: Published cohort or randomized controlled studies were retrieved from PubMed and Embase databases. Pooled standardized mean difference (SMD) with 95% confidence interval (CI) was calculated in a random effects model.

RESULTS: Six studies involving 221 COPD patients were included. Pooled effect size showed no significant improvements in FEV_1 (SMD: 0.28, 95% CI: -0.17 to 0.72, *p*=0.227), FVC (SMD: 0.54, 95% CI: -0.10 to 1.18, *p*=0.597) and FEV_1/FVC (SMD: 0.18, 95% CI: -0.09 to 0.46, *p*=0.189) in COPD patients after LTRA treatment. In subgroup analysis, neither short-term (<1 year) (SMD: 0.47, 95% CI: -0.06 to 0.99, *p*=0.082) nor long-term (≥1 year) (SMD: -0.13, 95% CI: -0.57 to 0.31, *p*=0.561) LTRA exposure could benefit lung function decline in COPD.

CONCLUSIONS: This meta-analysis suggests neither short-term nor long-term exposure of LTRA can improve lung function decline in COPD. However, large scale randomized controlled trials are urgently warranted.

Key Words:
Chronic obstructive pulmonary disease, Leukotriene receptor antagonists, Lung function, Meta-analysis.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by persistent airflow limitation owing to chronic inflammatory response to cigarette smoke and other noxious particles/gases, which eventually results in progressive lung function decline[1]. Leukotriene (LT), the proinflammatory mediator derived from 5-lipoxygenase activity, is functionally involved in the mechanism of asthma by stimulating cysteinyl leukotriene (CysLT) receptor. Leukotriene receptor antagonists (LTRA) have been approved by the Food and Drug Administration to relieve symptoms of asthma for decades. All three LTRA (zarfilukast, pranlukast and montelukast) are precisely active against the cysteinyl leukotrienes by blocking CysLT1 receptor[2]. Noticeably, recent studies reported high levels of LTB4 in sputum, BALF and lung tissue in COPD patients, which were associated with emphysema and lung/systemic inflammation[3,4]. Moreover, CysLT1 receptor-positive inflammatory cells are present in the bronchial mucosa in COPD, especially those experiencing severe exacerbations[5]. These data indicate LTB4-CysLT1 pathway may play an important role in COPD. Owing to an anti-inflammatory and bronchodilator effect of LTRA, several studies revealed improvements in complaints of shortness of breath and sputum production, as well as reduction in exacerbations and hospitalizations in COPD after LTRA treatment[6-8]. However, the impact of LTRA on lung function impairment in COPD was inconclusive with inconsistent results[6-12]. Meta-analysis has been considered to be a useful mean to pool the independent statistical powers and thus achieve a quantitative understanding of inconsistent results. Therefore, we performed this meta-analysis to draw a pooled conclusion on the effect of LTRA on lung function impairment in COPD.

Materials and Methods

Search Strategy

To identify all published studies relevant to LTRA and COPD, literature search was performed

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using the databases including PubMed and Embase. The search terms used were: 1) leukotriene receptor antagonist, cysteinyl leukotriene receptor antagonist, CysLT receptor antagonist, LTRA, zafirlukast, montelukast or pranlukast 2) COPD, chronic obstructive pulmonary disease, chronic obstructive airway disease or chronic airway disease (Figure 1).

Data extraction

Two independent reviewers collected the data according to inclusion and exclusion criteria. Inclusion criteria were retrieved cohort or randomized controlled studies detailed informed lung function alteration of COPD patients exposed to LTRA. Exclusion criteria were: 1) subjects with COPD and asthma overlap syndrome (ACOS); 2) not cohort or randomized controlled studies; 3) not human study; 4) duplicated report; 5) meeting abstract; 6) review articles with no useful data. Unpublished data were not considered. Disagreement was resolved by discussion before reaching a consensus.

Quality Assessment

To assess the quality of the included studies, two reviewers independently rated the studies according to the Newcastle-Ottawa Scale (NOS) for cohort studies and Jadad Scale for randomized controlled studies[13]. The 9-point NOS contains three items: selection (0-4), comparability (0-2), and exposure (0-3). Studies scored over 7 points on the NOS were deemed to be of high quality. The 5-point Jadad Scale also contains three items: randomization (0-2), blinding (0-2), and withdrawals/dropouts (0-1). Studies that scored over 3 points on the Jadad Scale were considered to be of high quality. When disagreement existed between the two reviewers, a discussion would be carried out.

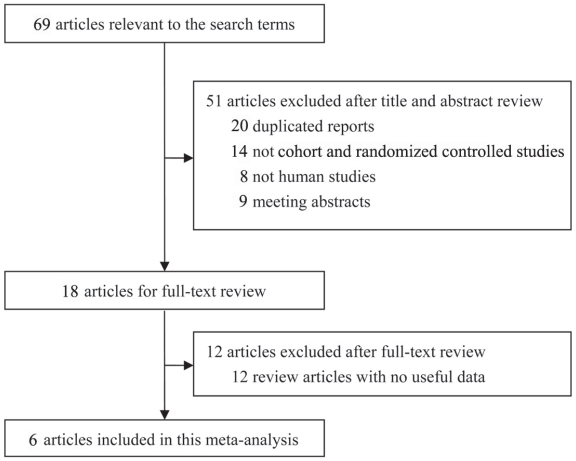

Figure 1. Flow diagram of search process.

Statistical Analysis

Continuous variables were presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs). Pooled SMD with 95% CI was calculated and $p<0.05$ was accepted with statistical significance. Heterogeneity was checked by the Q-test. Meta-analysis was done with the fixed-effects model when there was no heterogeneity ($p\geq0.1$). Otherwise, the random-effects model was used. The leave-one-out sensitivity analysis was performed by removing one study each time to check if individual study influenced the pooled results. Funnel plots, as well as the Begg's rank correlation test and Egger's linear regression test, were used to inspect the potential publication bias, and $p<0.05$ was considered significant publication bias. All analyses were conducted using Stata 11.0 (Stata Corp LP, College Station, TX, USA).

Results

Characteristics of Included Studies

Sixty-nine studies were relevant to the search terms. After reviewing the titles, abstracts and articles, sixty-three studies were exclude and only six studies matched the inclusion criteria. Noticeably, Cazzola et al[11,12] performed two studies with overlapped data about the effect of zafirlukast on lung function in the same COPD group. So, according to the exclusion criteria, one of the studies was excluded. The six included studies were carried out in Argentina, Italy, Iran, USA, Turkey, respectively[6-11]. The main features of the studies included in this meta-analysis were presented in Table I.

Quantitative Synthesized Results

Pooled effect size showed no significant improvements in FEV_1 (SMD: 0.28, 95% CI: -0.17 to 0.72, p=0.227) (Figure 2), FVC (SMD: 0.54, 95% CI: -0.10 to 1.18, p=0.597) (Figure 3) and FEV_1/FVC (SMD: 0.18, 95% CI: -0.09 to 0.46, p=0.189) (Figure 4) in COPD patients after LTRA treatment. In subgroup analysis, neither short-term (<1 year) (SMD: 0.47, 95% CI: -0.06 to 0.99, p=0.082) nor long-term (≥1 year) (SMD: -0.13, 95% CI: -0.57 to 0.31, p=0.561) LTRA exposure could benefit lung function decline in COPD (Figure 2).

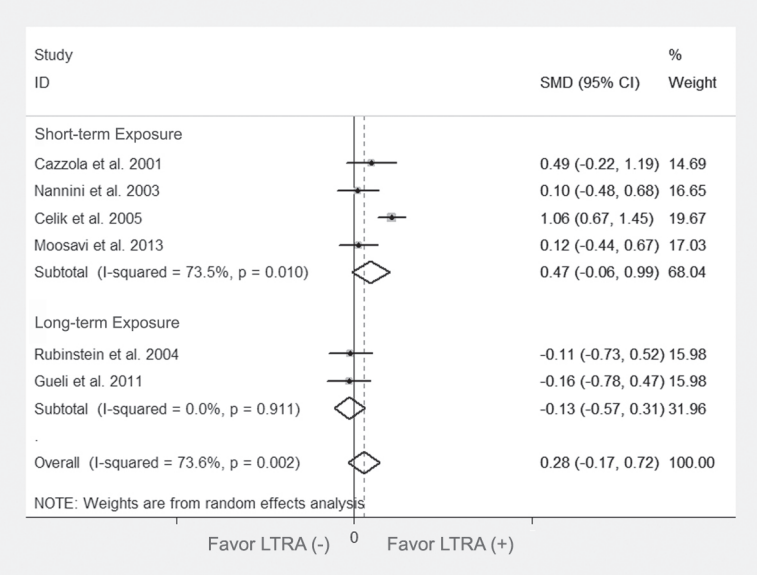

Figure 2. Forest plots of SMD with 95% CI for the effect of LTRA on FEV1 in COPD patients.

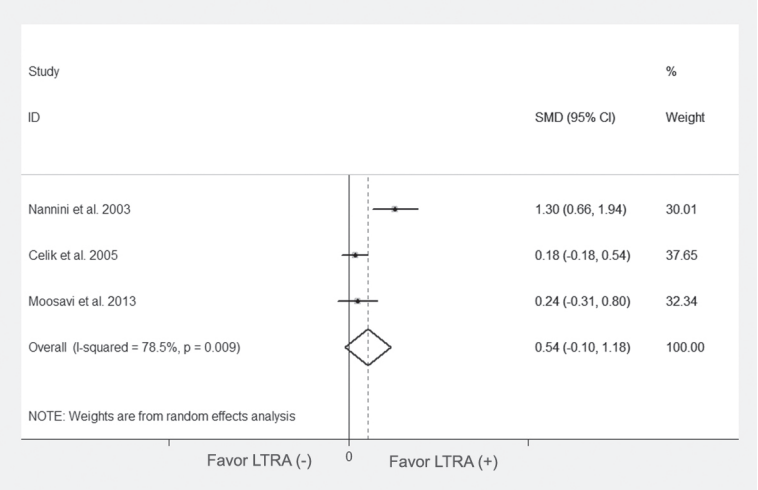

Figure 3. Forest plots of SMD with 95% CI for the effect of LTRA on FVC in COPD patients.

Heterogeneity and Sensitivity and Publication Bias

Significant heterogeneity was revealed among all studies in the meta-analysis. To identify the source of heterogeneity, subgroup analyses were performed according to the duration of LTRA treatment. No significant heterogeneity was revealed in the long-term exposure subgroup (p=0.911). Further, the leave-one-out sensitivity analysis was performed to check the influence of individual study on the pooled results. No significant alterations in pooled results were demonstrated after removal of all included studies one by one. Interestingly, after removal of the study by Celik et al[7], the overall heterogeneity was diminished (p=0.700). Although the funnel plots showed some asymmetry in the studies (Figure 5), publication bias was not suggested by Begg's rank correlation test (p=0.260) and Egger's linear regression test (p=0.054).

Discussion

LTRA, the anti-inflammatory agents, have been approved in asthma treatment for decades.

Table I. Clinical features of included studies.

References	Country	Study design	Subjects	Gender (M/F)	Age	Smoking (Pack-years)	LTRA Treatment	LFT		Combined Therapy	Quality score	
								LTRA	Baseline/Control		NOS	JAD
Cazzola et al[11,12]	Italy	Randomized double-blind double-dummy crossover controlled	16 (moderate to severe) stable COPD	12/4	66.30±5.85	>10	Zafirlukast 40 mg SD 130 min	FEV_1 (l)=1.40±0.38	FEV_1 (l)=1.22±0.36	Inhaled salmeterol		3
Nannini et al[9]	Argentina	Randomized double-blind crossover placebo-controlled	23 (moderate to severe) stable COPD	16/7	59.40±1.67	60.7±5.2	Zafirlukast 40 mg SD 90 min	FEV_1 (l)=0.81±0.64 FVC (l)=1.76±0.10	FEV_1 (l)=0.75±0.55 FVC (l)=1.63±0.10	NR		3
Rubinstein et al[6]	USA	Cohort	20 (moderate to severe) stable COPD	NR	71.20±10.70	NR	Montelukast 10 mg QD 2 years	FEV_1% pred=40±20 FEV_1/FVC% pred=57±17	FEV_1% pre=42±18 FEV_1/FVC%pred=57±11	Prednisone; Inhaled bronchodilators; ICS	7	
Celik et al[7]	Turkey	Randomized single-blind prospective controlled	117 stable COPD LTRA (+)=58 LTRA (-)= 59	100/17	65.72±9.11	LTRA(+): 51.5±31.7 LTRA(-): 51.2±37.9	Montelukast 10 mg QD 2 months	$^{\Delta}FEV_1$ (l)=0.17±0.16 $^{\Delta}FVC$ (l)=0.09±0.23 $^{\Delta}FEV_1$/FVC%=0.16±0.26	$^{\Delta}FEV_1$ (l)=0.02±0.12 $^{\Delta}FVC$ (l)=0.05±0.21 $^{\Delta}FEV_1$/FVC%=0.12±0.25	Ipratropium bromide; Formoterol		2
Gueli et al[8]	Italy	Cohort	20 stable COPD	15/5	72.80±6.30	NR	Montelukast 10 mg QD 1 year	FEV_1% pred=75.0±25.1	FEV_1% pred=79.5±32.4	Inhaled β2-agonists	8	
Moosavi et al[10]	Iran	Cohort	25 (moderate to severe) sable COPD	NR	67.29±5.56	>10	Zafirlukast 40 mg QD 2 weeks	FEV_1 (l)=1.05±0.35 FVC (l)=1.56±0.51 FEV_1/FVC% pred=68.29±30.14	FEV_1 (l)=1.01±0.33 FEV_1/FVC% pred=58.96±14.39 FVC (l)=1.44±0.47	NR	7	

NR=not reported; M=male; F=female; LTRA= Leukotriene receptor antagonists; LFT=lung function test; SD=single dose; QD=quaque die; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; Pred=predicted; NOS=Newcastle-Ottawa Scale; JAD=Jadad Scale; ICS=inhaled corticosteroids.

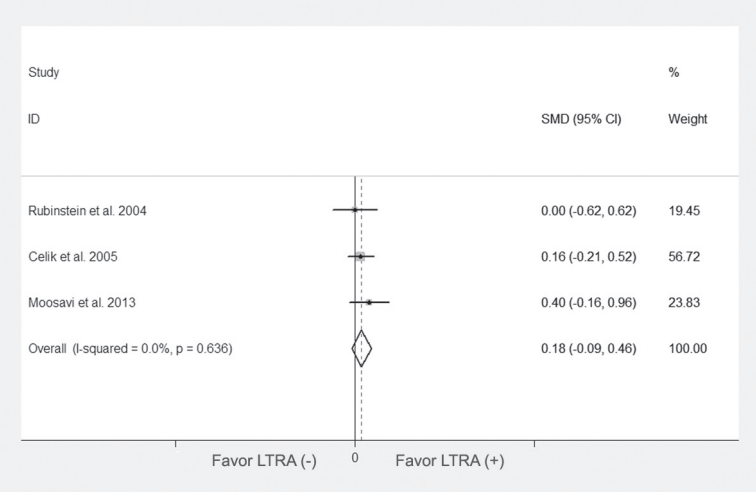

Figure 4. Forest plots of SMD with 95% CI for the effect of LTRA on FEV1/FVC in COPD patients.

Moreover, new therapeutic value of LTRA in COPD recently emerged with attenuations in inflammatory levels, symptoms, exacerbations and hospitalizations[6-8]. However, the effects of LTRA on lung function decline in COPD were not determined with inconsistent results. In this meta-analysis, even combined with bronchodilators and/or corticosteroids, no significant improvements in lung function (FEV_1, FVC, FEV_1/FVC) in COPD were found after LTRA treatment, and neither short-term nor long-term LTRA exposure could benefit lung function decline in COPD. Significant heterogeneity was revealed among all studies in the meta-analysis, which was diminished in the long-term exposure subgroup and after removal of the study by Celik et al[7]. Differences in duration of LTRA exposure and study design, sample size, and statistic methods in the study by Celik et al[7], may contribute to the overall heterogeneity. However, the heterogeneity had no significant impact on the pooled results, which was persistent in the sensitivity analysis. When applying the results in the present study, some limitations should be taken into account. Firstly, although the ACOS was excluded in this meta-analysis, it was very difficult to make sure the airway responsiveness for every subject included was normal, because of lack of the data involving bronchial provocation/dilation test. Secondly, the included studies had small sample size and might not have adequate statistic power. Lastly, the pooled estimates in this meta-analysis were not based on adjustment by potential confounded factors, such as age, gender, smoking history, nationality, combined therapy, etc.

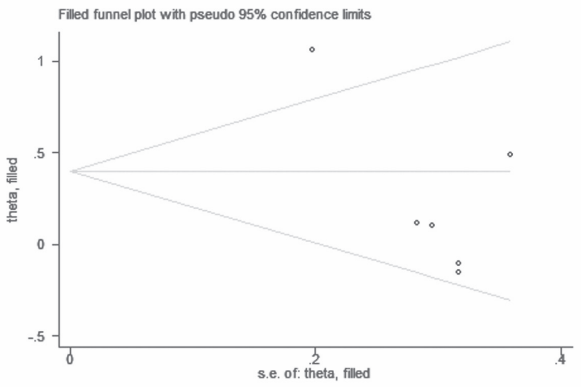

Figure 5. Begg's funnel plots for evaluation of publication bias for the effect of LTRA on FEV1 in COPD patients.

Conclusions

Our meta-analysis cautiously suggests neither short-term nor long-term exposure of LTRA has no positive effect on lung function decline in COPD, although some benefits of LTRA were reported in relief of inflammatory response, symptoms, exacerbations and hospitalizations in COPD[14]. Consequently, as for improving lung function impairment in COPD, LTRA are not recommended. However, large scale randomized controlled trials are needed to verify the results in this meta-analysis.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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