

Comparison of Leukotriene Receptor Antagonist and Theophylline in Addition to Inhaled Corticosteroid in Adult Asthma: A Meta-Analysis

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Abstract

This meta-analysis was performed to evaluate the difference of the therapeutic efficacy and adverse effects of leukotriene receptor antagonist and theophylline added to inhaled corticosteroids in adult asthma. Databases were searched for studies published through Nov, 2010. Randomized-controlled trials containing inhaled corticosteroids plus leukotriene receptor antagonist and inhaled corticosteroids plus sustained-release theophylline for asthma therapy were selected. For each report, data were extracted to the outcomes analyzed: mean change in morning peak expiratory flow, mean change in evening peak expiratory flow, mean change in morning forced expiratory volume in 1 sec, mean change in daily short beta₂-agonist use, asthma exacerbation and adverse effects. Four assessable trials including 182 asthmatic patients were identified. Inhaled corticosteroids plus leukotriene receptor antagonist was superior to inhaled corticosteroids plus theophylline therapy in improving morning peak expiratory flow in asthmatics (mean difference 19.08 [95% confidence interval 13.37-23.79] l/min, $p < 0.001$) and morning forced expiratory volume in 1 sec in asthmatics (mean difference 0.09 [95% confidence interval 0.03-0.14] liter, $p = 0.001$). In evening peak expiratory flow, daily short beta₂-agonist use, asthma exacerbation and adverse effects, there was no significant difference between these two therapies (All $p > 0.05$). Our meta-analysis showed that the combination of inhaled corticosteroids plus leukotriene receptor antagonist resulted in more improvement in both peak expiratory flow and forced expiratory volume in 1 sec in the morning than inhaled corticosteroids plus sustained-release theophylline in adult asthmatics. Further trials are necessary to evaluate the dominant effects of the former combination.

Key Words: Asthma, Meta-analysis, Leukotriene receptor antagonist, Theophylline, Inhaled corticosteroids

INTRODUCTION

Asthma is a disorder of the intrapulmonary airways characterized by variable airflow obstruction and airway hyper-responsiveness to various environmental or inherent stimuli. In the majority of patients, mild to moderate asthma airway dysfunction is usually responsive to inhaled corticosteroids (ICS) that form the mainstay of therapy (Fanta, 2009). In fact, asthmatic symptoms are well controlled by ICS alone in many cases, but other patients with persistent asthma require additional medications.

At present, alternative controller medications include long-acting β_2 agonists (LABA), leukotriene receptor antagonist (LTRA) and sustained-release theophylline. LABA significantly improve pulmonary function in patients with uncontrolled

asthma as add-on therapy to ICS compared with LTRA and theophylline (Davies *et al.*, 1998; Moore *et al.*, 1998). Since LABA do not have definite anti-inflammatory effects, there are little concerns about enhancing airway remodeling by LABA (Vanacker *et al.*, 2002). Further more, inhaled medicine may fail to reach small airways, the site of inflammation in moderate to severe asthmatic patients (Mcivor *et al.*, 1998).

Both LTRA and theophylline have anti-inflammatory effects, and can reach the small airway via the bloodstream, so they may be also the suitable choice (Spina *et al.*, 1998; Lipworth, 1999). In an early small randomized controlled trial (RCT), in patients who still have symptoms on treatment with ICS, the addition of LTRA or sustained-release theophylline to the treatment had similar results in benefits and adverse effects (Yurdakul *et al.*, 2002). Since then, the comparison of

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LTRA and sustained-release theophylline in addition to ICS has been evaluated in several other RCTs, and the results were not very consistent. Thus, the objective of the present meta-analysis was to evaluate the difference of the therapeutic efficacy and adverse effects of LTRA and sustained-release theophylline added to ICS in asthma.

MATERIALS AND METHODS

Data sources and searches

Two investigators (Huijuan Fang and Di Jin) searched MEDLINE, EMBASE, LILACS, and CINAHL databases for relevant articles published until Nov, 2010, no lower date limit was applied. The first MEDLINE search strategy retrieved citations containing the “leukotriene receptor antagonist OR montelukast OR pranlukast OR zafirlukast” and “theophylline” and “inhaled corticosteroids” and “asthma*” (Limits Activated: Randomized Controlled Trial). We modified these searches for the other databases. We screened reference lists from all retrieved articles and from recent review articles to identify additional studies. There were no language restrictions. Results were double-checked and arbitrated by a second investigator (Weining Xiong).

Study selection

We included full-text publications that investigated adult patients with asthma during treatment with ICS, including LTRA or sustained-release theophylline as the second medications.

Data extraction and quality assessment

To avoid bias in the data-abstraction process, two observers independently abstracted information about participants, interventions, and comparisons from publications, including mean change in morning peak expiratory flow (PEF), mean

change in evening PEF, mean change in morning forced expiratory volume in 1 second (FEV_1), mean change in daily short β_2 -agonist use, asthma exacerbation and adverse effects. Another reviewer double-checked the information. In the data-abstraction process for each trial that we identified, if the trial had none of the relevant information mentioned above, then the trial was excluded from the analysis for that information. In addition, for each trial, data defined according to criteria that varied from that mentioned above also were considered no evaluable. All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators.

We assessed the trials in terms of their risk of bias, according to the following domains: allocation of randomization sequence, concealment of allocation, blinding, handling of withdrawals, selective reporting, and other bias (such as inconsistencies in the baseline). Each entry is divided into yes, probably yes or no, but concealment of allocation is divided into yes, probably yes, unclear or no. Each of these quality domains was scored on a 3-point scale. Trials received an A score when all quality criteria for the domain were met, a B score when the criteria were partially met, and a C score when the criteria were not met (Schulz *et al.*, 1995; Jadad *et al.*, 1996).

Statistical analysis

For outcomes where data are reported as binary event data, we have pooled studies with a fixed-effect risk ratio (RR). However, where studies have reported no events occurring and thus contribute zero event rates to analyses, 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% confidence intervals (CIs) (DerSimonian

Table 1. The characteristics of subjects studied

Study	Design/Methods	Participants	Interventions (addition to ICS)	Duration of trial, wks	Outcomes
Yurdakul, 2002	A randomized study	64 patients with moderate persistent asthma	Formoterol vs. zafirlukast vs. theophylline	4, 8, 12 (3 time point and 8 chosen)	Mean change in number of daily short β_2 -agonist use, asthma exacerbation and adverse effects others
Dempsey, 2002	A randomized single-blind, placebo controlled, double dummy, three-way crossover study	24 patients with middle- moderate persistent asthma	High dose ICS vs. zafirlukast vs. theophylline	4 (one stage)	Mean change in morning PEF, mean change in evening PEF, mean change in morning FEV_1 others
Tsuchida, 2005	A single blind, randomized, multicenter study	67 patients with moderate or severe persistent asthma	Pranlukast vs. theophylline	4	Mean change in morning PEF, mean change in evening PEF, mean change in number of daily short β_2 -agonist use others
Shah, 2006	A randomized, double-blind study	90 patients with asthma	High dose ICS vs. Montelukast vs. theophylline	8	Mean change in morning PEF, mean change in morning FEV_1 , mean change in number of daily short β_2 -agonist use, asthma exacerbation others

and Laird, 1986).

For quantitative and continuous data variables we have 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 have pooled using a fixed-effect standardized mean difference (SMD). Where possible, for each end point, we combined the results from individual studies to produce summary effect estimates. Heterogeneity was calculated with the Cochrane Q statistic test and the I^2 test (Deeks *et al.*, 2001; Higgins *et al.*, 2003). Based on the statistical significance of heterogeneity test ($p>0.10$), a fixed-effect model was applied in our meta-analysis (DerSimonian and Laird, 1986).

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

RESULTS

Study characteristics and quality

After independent review, four RCTs including the compar-

son of LTRA and theophylline in addition to ICS in asthmatic adults were considered to be eligible for inclusion in the analysis (Dempsey *et al.*, 2002; Yurdakul *et al.*, 2002; Tsuchida *et al.*, 2005; Shah *et al.*, 2006), all available for analysis, and their characteristics are listed in Table 1. Totally, 90 patients were randomly assigned to LTRA addition to ICS and 92 patients were assigned to theophylline addition to ICS groups. As shown in Table 2, the quality scores of all these 4 studies were high, three studies reached A, and remaining one reached grade B.

Outcomes

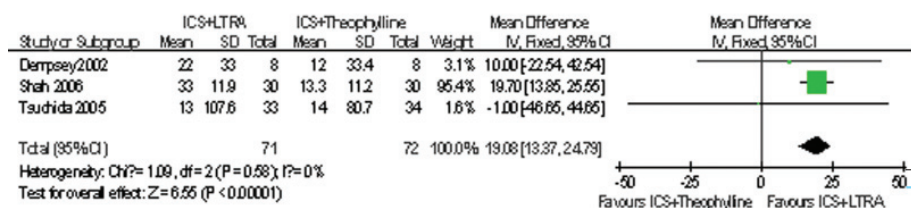
Mean change in morning PEF (L/min): 143 patients from three studies were considered for this analysis (71 treated with ICS plus LTRA, 72 treated with ICS plus theophylline) (Dempsey *et al.*, 2002; Tsuchida *et al.*, 2005; Shah *et al.*, 2006). ICS plus LTRA was superior to ICS plus theophylline therapy in improving morning PEF in asthmatics (mean difference 19.08 [95% CI 13.37-23.79] l/min, $p<0.001$) (Fig. 1). No significant inter-study heterogeneity was found ($I^2=0$, $p=0.58$).

Mean change in evening PEF (L/min): 83 patients from two studies were considered for this analysis (41 treated with ICS

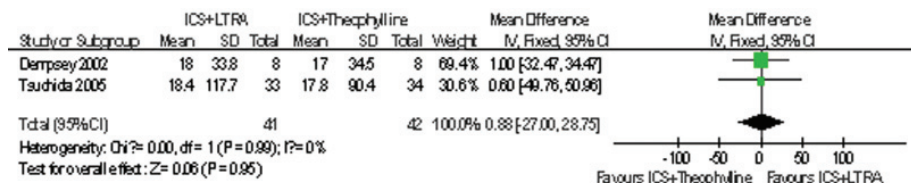
Table 2. Quality scores

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Baseline characteristics	Free of selective reporting	Free of other bias	Grade
Yurdakul, 2002	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	B
Dempsey, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	A
Tsuchida, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	A
Shah, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	A

A Mean change in morning peak expiratory flow (l/min)



B Mean change in evening peak expiratory flow (l/min)



C Mean Change in morning forced expiratory volume in 1 second (liter)

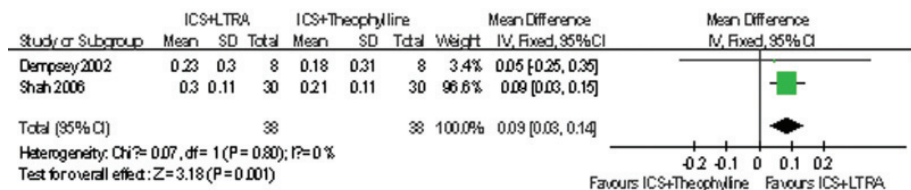
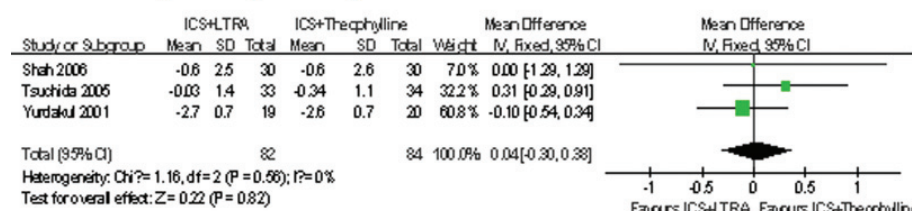
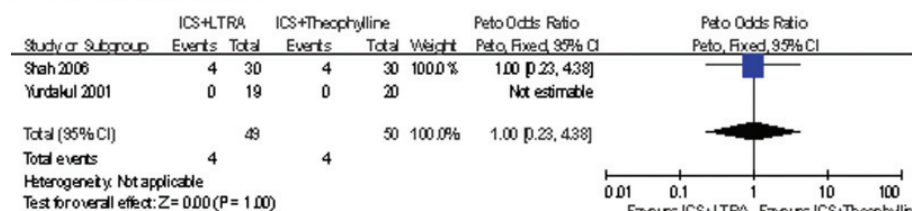


Fig. 1. Summary effect on mean change in morning peak expiratory flow (L/min), evening peak expiratory flow (L/min) and morning forced expiratory volume in 1 second (liter). ICS means inhaled corticosteroids, LTRA means leukotriene receptor antagonist.

A Mean change in daily beta2-agonist use



B Asthma exacerbation



C Adverse effects

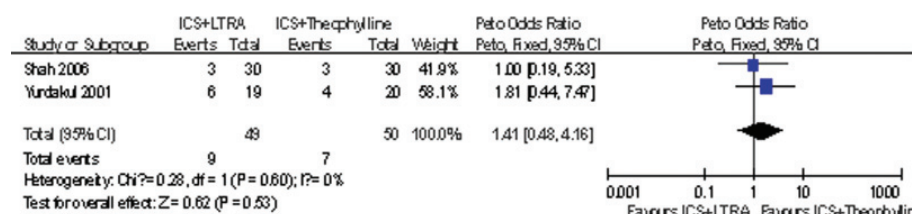


Fig. 2. Summary effect on mean change in daily beta2-agonist use, asthma exacerbation and adverse effects. ICS means inhaled corticosteroids, LTRA means leukotriene receptor antagonist.

plus LTRA, 42 treated with ICS plus theophylline) (Dempsey *et al.*, 2002; Tsuchida *et al.*, 2005). There was no significant difference between ICS plus LTRA and ICS plus theophylline therapy in improving evening PEF in asthmatics (mean difference 0.88 [95% CI -27.00-28.75], $p=0.95$) (Fig. 1). No significant inter-study heterogeneity was found ($I^2=0$, $p=0.99$).

Mean change in morning FEV₁ (liter): 76 patients from two studies were considered for this analysis (38 treated with ICS plus LTRA, 38 treated with ICS plus theophylline) (Dempsey *et al.*, 2002; Shah *et al.*, 2006). ICS plus LTRA was superior to ICS plus theophylline therapy in improving morning FEV₁ in asthmatics (mean difference 0.09 [95% CI 0.03-0.14] liter, $p<0.001$) (Fig. 1). No significant inter-study heterogeneity was found ($I^2=0$, $p=0.80$).

Mean change in number of daily short β_2 -agonist use: 166 patients from three studies were considered for this analysis (82 treated with ICS plus LTRA, 84 treated with ICS plus theophylline) (Yurdakul *et al.*, 2002; Tsuchida *et al.*, 2005; Shah *et al.*, 2006). There was no significant difference between ICS plus LTRA and ICS plus theophylline therapy in reducing the number of daily β_2 -agonist use in asthmatics (mean difference 0.04 [95% CI -0.30-0.38], $p=0.82$) (Fig. 2). No significant inter-study heterogeneity was found ($I^2=0$, $p=0.56$).

Asthma exacerbations: Data on asthma exacerbations were available in two trials (49 treated with ICS plus LTRA, 50 treated with ICS plus theophylline) (Yurdakul *et al.*, 2002; Shah *et al.*, 2006). Asthma exacerbations were almost equal between ICS plus LTRA and ICS plus theophylline therapy in asthmatics (pooled OR 1.00 [95% CI 0.23-4.38], $p=1.00$) (Fig. 2). The heterogeneity was not applicable.

Adverse effects: 99 patients from two studies were consid-

ered for this analysis (49 treated with ICS plus LTRA, 50 treated with ICS plus theophylline) (Yurdakul *et al.*, 2002; Shah *et al.*, 2006). There was no major adverse reactions noted, and no significant difference between ICS plus LTRA and ICS plus theophylline therapy in minor adverse events in asthmatics (pooled OR 1.41 [95% CI 0.48-4.16], $p=0.53$) (Fig. 2). No significant inter-study heterogeneity was found ($I^2=0$, $p=0.60$).

DISCUSSION

The objectives of effective asthma management are to prevent chronic or frequently recurring symptoms, to maintain normal pulmonary function and normal activity levels, to prevent recurrent acute exacerbations and avoid adverse effects from asthmatic medications (NIH, 2002). In some cases, especially in persistent asthma, these objectives are sometimes not fully fulfilled with ICS alone. For this purpose, in addition to ICS, we discussed the efficacy of the second controller medications in the treatment of asthma. Within the currently available add-on medications, LABA probably shows the strongest bronchodilator effects and is the first-line therapy in persistent asthma in combination with ICS (NIH, 2002). In asthmatic adults on low doses of ICS, the addition of LABA is superior to LTRA or theophylline for asthma control (Ducharme *et al.*, 2006; Tee *et al.*, 2007). However, LABA is not primarily an anti-inflammatory drug, and does not appear to have any clinically important anti-inflammatory or proinflammatory effect (Sindi *et al.*, 2009). Furthermore, the effect of LABA on airway remodeling remains controversial (Orsida *et al.*, 2001; Vanacker *et al.*, 2002). Thus, LTRA or theophylline as the add-on medication

to ICS should be reconstructed.

It has been reported that add-on therapy with LTRA or theophylline to ICS significantly improved lung function and asthmatic symptoms in comparison with an increased dose of ICS (Evans *et al.*, 1997; Price *et al.*, 2003). Then, which add-on agent is better? In the current meta-analysis, we found that ICS plus LTRA therapy was superior to ICS plus theophylline therapy in improving morning PEF and FEV₁, measures that are commonly used for quantifying asthma control. In other indexes, such as evening PEF, daily short β₂-agonist use, asthma exacerbation and adverse effects, there is not significant difference between these two therapies.

Owing to very limited studies were available for inclusion in this meta-analysis, we could not examine the effect of study quality on the main endpoints in the treatment of asthma with LTRA or theophylline. For the same reason, we could not investigate whether or not study size, agents (different LTRA or different ICS), or duration of treatment affect the evaluation of LTRA or theophylline. Because of inconsistent results reported among the trials, some comparisons had to be restricted to patients for whom results were available instead of using all patients. In our meta-analysis, although ICS plus LTRA therapy was superior to ICS plus theophylline therapy in improving morning PEF and FEV₁, we could find that in the three studies included in the analysis for these two indexes, one study (Shah *et al.*, 2006) had a too large weight caused by other two studies (Dempsey *et al.*, 2002; Tsuchida *et al.*, 2005) due to their excessive standard deviation. Thus, this conclusion should be regarded cautiously.

The trials included in this meta-analysis showed a wide variation in size or the treatment regimens used, and relative small sample size. We noted that different LTRA, such as montelukast, pranlukast, zafirlukast, were used in different studies and different ICS, such as budesonide and beclomethasone, were used in different studies, although they have similar efficacy. Fortunately, the inspection about heterogeneity indicated that the heterogeneity in our study did not reach the level of significance.

In conclusion, our meta-analysis showed that the combination of ICS plus LTRA resulted in more improvement in both PEF and FEV₁ in the morning than ICS plus sustained-release theophylline in asthmatics, but in evening PEF, daily short β₂-agonist use, asthma exacerbation and adverse effects, there was no significant difference between these two therapies. Based on the limits of this meta-analysis, we call for future works about the comparison of LTRA and sustained-release theophylline in addition to ICS in the form of larger, multicentre, randomized controlled trials adequately to evaluate this therapeutic option in patients with persistent asthma.

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