ORIGINAL ARTICLE

The comparative effect of Leukotriene receptor antagonist add on therapy and step up inhaled Corticosteroid in partially controlled asthma: An open-labeled randomized controlled trial

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Abstract

**Background:** No studies are comparing the impact of the add-on leukotriene-receptor antagonist (LTRA) with a step-up dose of inhaled corticosteroids (ICS) in partly controlled asthma patients with asthma control test (ACT) score < 23. 

**Objective:** To study the effect of LTRA add-on therapy in comparison to a step-up to medium dose of ICS in partially controlled asthma.

**Methods:** An open-labeled randomized controlled trial was conducted in asthma subjects with partly controlled asthma who had been in regular receipt of low dose ICS. All subjects were assessed for asthma using ACT, daytime and nighttime symptoms, rate of relievers used, spirometry, and impulse oscillometry (IOS) at 3 and 6 months. Subjects were randomized to receive daily oral LTRA 10 mg or step-up medium dose of ICS.

**Results:** Between June 2020 and January 2021, 50 participants were enrolled, all patients completing the study. After treatment, mean ACT scores were increased to more than 23 indicating well-controlled asthma in both groups, control being sustained throughout the whole 6-month study period (P < 0.001). Within each group, ACT scores were improved by a minimal clinical important difference (MCID) ≥ 3 points at 6 months, compared to baseline values. There were significant decreases in nighttime and daytime symptoms, and the numbers of rescue relievers used in 4 weeks in both groups compared to baseline (P < 0.001).

**Conclusions:** LTRA add-on therapy in partially controlled asthma patients is comparable with step-up to medium dose of ICS/LABA as regards asthma control.

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**KEYWORDS**
Asthma; asthma control; inhaled corticosteroids; leukotriene-receptor antagonists; lung function

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Introduction

Asthma is a common chronic disease and a major public health problem globally and in Thailand. It is characterized by various symptoms such as wheeze, shortness of breath, chest tightness, cough, and the limitations in variable expiratory airflow. According to the Global Initiative for Asthma (GINA), there are approximately 300 million people worldwide with this disease. In Thailand, the prevalence of asthma in adults has been recorded as being between 3% and 7%.

Leukotrienes are the mediators involved in the inflammation associated with asthma, different types of inflammatory cells including mast cells, eosinophils, basophils, macrophages, and monocytes. Leukotrienes cause chronic inflammation of the respiratory mucosa by stimulating the white blood cells to release inflammatory substances. In adolescents and adults with asthma whose condition is not controlled with daily low-dose inhaled corticosteroids (ICS), the addition of anti-leukotriene agents to the ICS reduces the number of exacerbations requiring an oral corticosteroid by half. Anti-leukotrienes and ICS have also been shown to improve lung function, asthma control, and quality of life.

According to GINA guidelines, all patients with asthma, especially those with persistent asthma, at GINA step 2 should be regularly treated with ICS to establish control. ICS are used as the main therapy for disease control and should be started initially at a low dose. When ICS cannot be used, anti-leukotriene may be an alternative drug choice. If the patients do not meet symptom-controlled criteria, the step-up options are to increase ICS to a medium to high dose, adding sublingual immune therapy (SLIT), or adding a leukotriene receptor antagonist (LTRA). A previous study suggested that long-term use of high-dose ICS therapy, a dose equivalent to 250 to 500 mcg of fluticasone, has the potential to cause systemic side effects including diabetes mellitus (DM), decreased bone mineral density, skin thinning and bruising, and cataracts. Another study also showed that inhalation of fluticasone of more than 1000 mcg per day has greater risks of adrenal suppression and new-onset DM. However, a study by Rogala et al. has shown that ICS administered in low doses do not affect fasting glycemia. Thus, the effects of long-term use of ICS therapy in subjects with asthma on new-onset DM are still controversial.

To date, there is no comparative study between the add on LTRA and the step-up dose of ICS therapies in partly controlled asthmatic GINA step 2 patients in whom the asthma control test (ACT) score is less than 23. This study was designed to investigate the hypothesis that LTRA add on therapy was comparable to ICS step-up therapy. Therefore, the primary objective of this study was to explore the effect of LTRA add-on therapy in comparison to the step-up of ICS to medium dose in patients with partially controlled asthma. The secondary objective was to evaluate the effect of LTRA add-on therapy in comparison to the step-up of ICS to a medium dose in partially controlled asthma measured by spirometry, impulse oscillometry (IOS), nighttime, and daytime symptom control, and the number of relievers used.

Materials and Methods

Study design

This randomized controlled trial was conducted at the Airway Clinic, Lung Health Center, Division of Pulmonary, Critical Care and Allergy, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University.

Study population

Patients with partially controlled asthma aged ≥18 years old who received maintenance therapy of low dose ICS and fixed-dose LABA for GINA step 2 or 3 at the Airway Clinic, Division of Pulmonary, Critical Care, and Allergy, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University were enrolled into the study. The subjects who were enrolled in the study should have met at least one of the following criteria: if the pulmonary function test showed airflow limitations by measurement of less than 0.75 from the ratio of forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) and have bronchodilator reversibility measurements before treatment or after treatment for at least 4 weeks; subjects with a history of respiratory symptoms of ≥1 of the criteria including respiratory symptoms of wheeze, shortness of breath, cough, chest tightness, symptoms are often worse at night or in the early morning, symptoms varying over time and in intensity, symptoms are triggered by viral infections (colds), exercise, allergen exposure, change in weather, or irritants, smoke or strong smells were all included. Subjects with a history of severe exacerbation or hospitalization within 1 year were excluded. Pregnant or breastfeeding individuals, those with a history of systemic steroid administration in the last 6 months, treatment with long-acting muscarinic antagonist (LAMA) therapy, and a history of previous LTRA use in the previous 3 months were also excluded from the study.

Study procedure

Subjects who met the eligibility criteria were randomized using a computer-generating randomization program into one of two groups [add on LTRA or a step-up to moderate dose of ICS (budesonide or fluticasone) plus LABA (vilanterol, salmeterol, or formoterol)]. This procedure was necessary to ensure the concealment of the randomization. The entire randomization process was performed by a physical therapist who was not directly involved in the study. The ratio between the groups was 1:1. In the add-on LTRA treatment arm, subjects were prescribed 10 mg oral LTRA once a day. In the step-up ICS and fixed-dose LABA treatment arm, subjects were prescribed an increased dose of ICS from low to medium. All patients were allowed to use other add-on medications such as short-acting beta2-agonists (SABA) or theophylline. The research and reporting methodology followed the CONSORT guidelines. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University [Institutional...
Review Board (IRB) approval number: MED-2562-06835, date of approval: February 25 2020 and filed with the Clinical Trials Registry (Study ID: TCTR20200408006, date of approval: April 08 2020). Written informed consent was obtained from all subjects before enrollment.

All subjects were asked to complete a validated asthma-symptom ACT questionnaire in accordance with GINA guidelines, carried out a spirometry test and IOS at 2 weeks before the baseline visit. After the screening visit (week 2) and baseline visit (week 0), study assessments were conducted in the clinic at 3 and 6 months. These included spirometry testing which was performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 guidelines. IOS was performed in accordance with the ERS recommended standards, the Thai version of ACT, and a symptoms control questionnaire.

Data collection

Demographic data including gender, age, body weight, height, body mass index (BMI), and comorbidities were collected. ACT scores, rate of acute exacerbation leading to hospitalization or emergency room (ER) visit, daytime and nighttime asthma symptoms, and frequency of rescue reliever use were collected. Spirometry was carried out by all subjects using a spirometer (Vmax Encore 22, Care Fusion, Hoechberg, Germany) in accordance with the ATS/ERS guidelines. Spirometry data including FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, and forced expiratory flow at 25-75% of FVC (FEF25-75%) were collected. IOS was performed in all subjects using an IOS (Master Screen IOS, Viasys GmbH, Hoechberg, Germany). The subjects were asked to perform tidal breathing for 30–40 s via a mouthpiece that was connected to a loudspeaker which generates pressure oscillations composed of multiple frequencies, a minimum of three tests being performed following ERS standards. IOS parameters including resistance at 5 Hz (R5), resistance at 20 Hz (R20), heterogeneity of resistance (R5–R20), the area under reactance (A5), reactance at 5 Hz (X5), and frequency resonance (Fres) were also collected. Clinical and lung-function data were recorded by a technician who was blinded to this mode of treatment. All measurements were recorded at baseline, month 3, and month 6.

Definitions

Acute asthma exacerbation was defined as subjects who showed at least one of the clinical criteria including wheezing, shortness of breath, chest tightness, and wheezing during the examination which required administration of oral steroids and/or antibiotics.

Partly controlled asthma was defined as when an ACT score was less than 23 or the presence of at least one symptom in the symptoms assessment questionnaires in the past 4 weeks including ≥1 nighttime symptom, ≥2 daytime symptoms, ≥2 rescue reliever used, and ≥2 symptoms of limited activity.

Inhaled corticosteroid dose equivalence was taken as follows: a low dosage of ICS is equivalent to inhaled fluticasone propionate <250 mcg per day, medium dose ICS is equivalent to inhaled fluticasone propionate 250-500mcg per day, and high dose ICS is equivalent to inhaled fluticasone propionate >500 mcg per day.

Sample size estimation

We estimated an effect size of 0.3 which is equal to a moderate treatment effect. Thus, we needed 20 subjects per group for confident acceptance or rejection of the hypothesis (power = 0.8 with statistical significance < 0.05). However, a loss to follow-up rate of 20% was expected. Therefore, 25 subjects needed to be enrolled per group.

Statistical analysis

Results for numerical values were expressed as mean ± standard deviation and those for categorical data as absolute frequencies and percentages. Independent sample t-tests and Mann-Whitney U tests were used to analyze differences between baseline characteristics between the two groups for parametric and non-parametric data, respectively. Fisher’s exact test was used to compare the categorical data between groups. A 95% confidence interval (CI) was derived for the difference between mean scores. The MCID for the ACT was set at a score change ≥3 points. Repeated measures analysis of variance (ANOVA) was used to calculate statistically significant differences in ACT scores between the two groups. All analyses were carried out using SPSS, version 26.0 statistical software.

Results

Fifty-six subjects with asthma were recruited for the study. Six subjects who used a systemic steroid, inhaled LAMA, and declined to participate. Therefore, 50 subjects were randomized into the two groups, add on LTRA and step up to a moderate dose of ICS. The details are shown in Figure 1.

Subject demographic data and lung function are shown in Table 1. All subjects reported partial control of asthma symptoms on current treatment. All subjects had been prescribed a low dose of ICS and LABA before enrollment. Allergic rhinitis was the major comorbidity and was mostly of mild intermittent severity. There were no significant differences in baseline characteristics, spirometry, and IOS parameters between the two groups.

The ACT scores for all subjects were recorded at baseline and 3 and 6 months. There was no significant difference in the mean ACT scores between groups throughout the follow-up period (P = 0.558). In both groups, there were statistically significant improvements in ACT scores throughout the follow-up period (P < 0.001) (Figure 2). The mean ACT scores in both groups were greater than 23, which equate to well-controlled asthma. In addition, the mean ACT scores were improved by met MCID ≥ 3 points at 6 months for both groups when compared to baseline.

Secondary outcomes measured at month 6 including asthma exacerbations, nighttime and daytime symptoms, and the frequency of rescue reliever use in the past 4
weeks are shown in Table 2. There was no exacerbation in the entire 6-month period of the study, the rates of moderate to severe exacerbations, and ER visits were not reported. Nighttime symptoms and frequency of rescue reliever use in the past 4 weeks less than 2 in both groups denote asthma control. The spirometric data at month 6 for both groups are also shown in Table 2. There was no significant difference in spirometric data between groups. The IOS readings to measure airway resistance, reactance, and small airway disease are also shown in Table 2. There were no statistically significant differences in all IOS parameters between groups. There were no significant differences in R5-R20 parameters which reflect small airways disease between groups throughout the study period. In addition, there were no significant changes in R5-R20 throughout the study period in both groups (Figure 3).

Discussion

Our study found that the prescription of LTRA add-on therapy in cases of partially controlled asthma is comparable to the step-up ICS/LABA as regards the effect on asthma control. There was no significant difference in asthma control between groups throughout the follow-up period. The mean ACT scores in both groups were greater than 23, which equates to well-controlled asthma. In addition, the mean ACT scores were improved by meeting MCID ≥ 3 points at 6 months for both groups when compared to baseline.

Regular daily therapy with ICS with or without LABA is effective in reducing asthma exacerbation in asthma patients. According to current guidelines on asthma management and prevention, the use of ICS remains the preferred controller for persistent uncontrolled asthma. Patients with persistent asthma symptoms are typically managed by increasing the dose of ICS or adding a second therapeutic agent. However, increasing the dose of ICS may be associated with a number of potential side effects and higher doses may not necessarily result in more effective control of asthma symptoms in all patients. Therefore, the international guidelines recommend that if there is interrelation in the patients or ICS side effects, another recommendation is the use of add on LTRA plus low dose ICS. The addition of a second controlling agent with a complementary mechanism of action may be appropriate. To date, there is no study in Thailand to compare the impact of add-on LTRA therapy and a step-up dose of ICS in partly controlled asthma in GINA step 2 patients with an ACT score less than 23. This study is designed to investigate the hypothesis that LTRA add-on therapy has a comparable level of efficacy to ICS step-up therapy.

Our findings suggested that the addition of LTRA to ICS offers comparable asthma control to a step up to a medium dose of ICS with good efficacy, resulting in an ACT of more
Table 1 Baseline characteristics of subjects in add on LTRA group and step-up ICS group.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LTRA group (n = 26)</th>
<th>Step-up-ICS group (n = 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.96 ± 13.37</td>
<td>59.67 ± 11.95</td>
<td>0.496</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>14 (53.8)</td>
<td>18 (75.0)</td>
<td>0.119</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24.99 ± 4.88</td>
<td>24.02 ± 3.50</td>
<td>0.428</td>
</tr>
<tr>
<td>Age at diagnosis of asthma</td>
<td>36.62 ± 10.30</td>
<td>37.25 ± 13.28</td>
<td>0.850</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>Ex-smoker 5 (19.2)</td>
<td>4 (16.7)</td>
<td>0.814</td>
</tr>
<tr>
<td></td>
<td>Non-smoker 21 (80.8)</td>
<td>20 (83.3)</td>
<td>0.813</td>
</tr>
<tr>
<td>Smoking pack-years</td>
<td>0.81 ± 1.86</td>
<td>1.10 ± 2.65</td>
<td>0.656</td>
</tr>
<tr>
<td>Low dose ICS and fixed dose LABA used n (%)</td>
<td>26 (100)</td>
<td>24 (100)</td>
<td>1.000</td>
</tr>
<tr>
<td>Comorbid with AR, n (%)</td>
<td>19 (73.1)</td>
<td>15 (62.5)</td>
<td>0.423</td>
</tr>
<tr>
<td>Severity of AR</td>
<td>Mild intermittent, n (%)</td>
<td>19 (100)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>ACT score</td>
<td>21.08 ± 1.38</td>
<td>20.88 ± 1.26</td>
<td>0.593</td>
</tr>
<tr>
<td>Spirometry data</td>
<td>FEV1 (L)</td>
<td>2.06 ± 0.71</td>
<td>0.333</td>
</tr>
<tr>
<td></td>
<td>% predicted of FEV1</td>
<td>80.69 ± 17.38</td>
<td>0.286</td>
</tr>
<tr>
<td></td>
<td>FVC (L)</td>
<td>2.79 ± 0.91</td>
<td>0.201</td>
</tr>
<tr>
<td></td>
<td>% predicted of FVC</td>
<td>89.23 ± 13.75</td>
<td>0.466</td>
</tr>
<tr>
<td></td>
<td>FEV1/FVC (%)</td>
<td>74.04 ± 9.42</td>
<td>0.795</td>
</tr>
<tr>
<td></td>
<td>FEF25-75%</td>
<td>1.77 ± 1.08</td>
<td>0.323</td>
</tr>
<tr>
<td></td>
<td>% predicted of FEF25-75%</td>
<td>65.19 ± 35.98</td>
<td>63.50 ± 29.32</td>
</tr>
<tr>
<td>IOS parameters</td>
<td>R5 (KPa/l/s)</td>
<td>0.509 ± 0.240</td>
<td>0.887</td>
</tr>
<tr>
<td></td>
<td>R20 (KPa/l/s)</td>
<td>0.379 ± 0.141</td>
<td>0.963</td>
</tr>
<tr>
<td></td>
<td>R5-R20 (KPa/l/s)</td>
<td>0.130 ± 0.132</td>
<td>0.853</td>
</tr>
<tr>
<td></td>
<td>X5 (KPa/l/s)</td>
<td>-0.171 ± 0.089</td>
<td>0.615</td>
</tr>
<tr>
<td></td>
<td>Fes (Hz)</td>
<td>18.63 ± 7.01</td>
<td>0.489</td>
</tr>
<tr>
<td></td>
<td>AX (KPa/l)</td>
<td>1.290 ± 1.410</td>
<td>0.996</td>
</tr>
<tr>
<td>Nighttime symptoms in the past 4 weeks</td>
<td>0.88 ± 0.58</td>
<td>0.75 ± 0.79</td>
<td>0.497</td>
</tr>
<tr>
<td>Daytime symptoms in the past 4 weeks</td>
<td>2.69 ± 1.78</td>
<td>3.38 ± 2.10</td>
<td>0.220</td>
</tr>
<tr>
<td>Reliever use in the past 4 weeks</td>
<td>2.50 ± 1.20</td>
<td>2.83 ± 1.12</td>
<td>0.320</td>
</tr>
</tbody>
</table>

Note: Data are mean ± standard deviation (SD) unless designated as n (%).

AR: allergic rhinitis; ACT: asthma control test; BMI: body mass index; IOS: impulse oscillometry; ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; FEV1: Forced expiratory in the first second; FVC: forced vital capacity; FEF25-75%: forced expiratory flow at 25-75% of FVC; R5: resistance at 5 Hz; R20: resistance at 20 Hz; R5-R20: heterogeneity of resistance between R5 and R20; Fes: resonant frequency; X5, reactance at 5 Hz; AX, the area under reactance curve between 5 Hz and resonant frequency.

Figure 2 Change from baseline over 6 months in ACT score between LTRA and step-up ICS groups.

than 23 within 3 months and being maintained until 6 months. During the follow-up period (months 3 and 6), the ACT score in both groups improved more than 3 points that met MCID and the mean ACT score in both groups greater than 23. Our results were supported by two previous studies indicating that LTRA could significantly improve asthma control.13–14

The problems on the asthma-diary cards, daytime and nighttime symptoms, and SABA reliever use were all significantly lower in comparison to before enrollment in both groups but there were no statistically significant differences between groups. The reductions in the number of days with nighttime and daytime symptoms were progressive and similar in the two groups, findings consistent with the effects of LTRA and higher dose ICS in a previous study.15

Our results also showed no significant differences between groups at the end of the study in respect of spirometric and IOS parameters as secondary outcome measures, including FEVI, FVC, FEVI/FVC, FEF25-75%, airway resistance, and reactance. The steady increase in pulmonary function and the progressive decrease in asthma symptoms observed in our study cannot be explained by simple bronchodilation and may be consistent with the reported anti-inflammatory effects of LTRA in several indices of asthmatic inflammation, including eosinophil counts in peripheral blood, sputum, and lung tissue16 and decreased exhaled nitric oxide.16 Based on these findings, additional studies involving measurement of inflammatory markers such as sputum eosinophils and longer study periods will be needed to explore these phenomena further.17

In the case of IOS parameters, the heterogeneity of resistance (R5-R20) which reflects resistance in small airway disease, no differences were found between groups. But within the LTRA group, some improvement in small airway resistance was observed. The improvement seen was more than 0.7 kPa/L/s which equates to a near resolution of small airway resistance in some literature.17,22 However, we propose a longer study period in a future study to establish the reliability and investigate the continuity of the results.
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For example, spirometry and IOS parameters were not significantly different between groups and larger sample sizes should be investigated in the future to confirm or deny these findings. Lastly, our study included only patients with partially controlled asthma (GINA step 2 or 3) who were being treated by specialized chest physicians in a tertiary hospital. Therefore, the results of this study may not be generalizable to other GINA asthma classifications and other settings such as general practitioners or community hospitals.

**Conclusion**

The efficacy of the use of LTRA add-on therapy in partially controlled asthma is comparable to the step-up ICS/LABA as regards the impact on asthma control. Asthma control using ACT score changed more than MCID (≥3 points) in both groups.

**Acknowledgments**

We wish to thank all the research team, especially the nursing team of the Division of Pulmonary, Critical Care, and Allergy, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University who carried out the history taking and the spirometry in this study. We also wish to thank all patients enrolled in the study who completed the whole exercise despite not receiving any compensation.

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**Table 2** Asthma exacerbation, nighttime and daytime symptoms, reliever use, spirometry, and IOS parameters at month 6 in the follow-up period.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LTRA group (n = 26)</th>
<th>Step up ICS group (n = 24)</th>
<th>Mean difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma exacerbation</td>
<td>No AE</td>
<td>No AE</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nighttime symptoms in the past 4 wks (time/wk)</td>
<td>0.19 ± 0.56</td>
<td>0.29 ± 0.75</td>
<td>0.09 (−0.28, 0.48)</td>
<td>0.598</td>
</tr>
<tr>
<td>Daytime symptoms in the past 4 wks (time/wk)</td>
<td>2.23 ± 2.17</td>
<td>2.13 ± 2.27</td>
<td>0.36 (−0.91, 1.62)</td>
<td>0.574</td>
</tr>
<tr>
<td>Reliever used in the past 4 wks (time/wk)</td>
<td>0.92 ± 0.97</td>
<td>1.21 ± 1.17</td>
<td>0.29 (−0.33, 0.89)</td>
<td>0.355</td>
</tr>
</tbody>
</table>

**Spirometry data**

- FEV1 (L): 2.07 ± 0.71 vs. 1.82 ± 0.44, P = 0.25 (−0.59, 0.08)
- FVC (L): 81.42 ± 17.49 vs. 85.75 ± 19.50, P = 4.33 (−6.19, 14.85)
- % predicted of FVC: 73.81 ± 10.84 vs. 72.75 ± 9.71, P = 0.06 (0.02, 1.04)
- FEV1/FVC (%): 90.85 ± 14.68 vs. 96.21 ± 16.34, P = 5.36 (−3.46, 14.19)
- FEF25–75 (L/s): 1.79 ± 1.12 vs. 1.50 ± 0.74, P = −0.29 (−0.84, 0.25)
- % predicted of FEF25–75: 67.08 ± 37.83 vs. 65.04 ± 29.59, P = −0.29 (−21.46, 17.39)

**IOS parameters**

- R5 (KPa/l/s): 0.48 ± 0.22 vs. 0.47 ± 0.14, P = −0.10 (−0.11, 0.09)
- R20 (KPa/l/s): 0.35 ± 0.12 vs. 0.34 ± 0.09, P = −0.01 (−0.07, 0.05)
- R5-R20 (KPa/l/s): 0.14 ± 0.14 vs. 0.14 ± 0.09, P = −0.00 (−0.07, 0.07)
- X5 (KPa/l/s): −0.12 ± 0.09 vs. −0.15 ± 0.10, P = −0.03 (−0.08, 0.02)
- Fres (KPa/l/s): 18.05 ± 6.11 vs. 17.68 ± 5.27, P = −0.37 (−3.63, 2.88)
- AX (KPa/l): 1.17 ± 1.34 vs. 1.15 ± 0.96, P = −0.01 (−0.68, 0.65)

**Note:** Data are mean ± standard deviation (SD).

FEV1: Forced expiration in the first second; FVC: forced vital capacity; FEF25–75%: forced expiratory flow at 25-75% of FVC; R5: resistance at 5 Hz; R20: resistance at 20 Hz; R5-R20: heterogeneity of resistance between R5 and R20; Fres: resonant frequency; X5: reactance at 5 Hz; AX: the area under reactance curve between 5 Hz and resonant frequency.

**Figure 3** Change in R5–R20 throughout the study period between LTRA and step-up ICS groups.

The strength of our study is the confirmed finding that the addition of LTRA to ICS offers comparable asthma control to a step up to a medium dose of ICS. However, this study has some limitations. First, a placebo control group was not included in our study which should be rectified in the future investigation. Second, there was no blinding treatment in either group with reference to the type of inhaler device and LTRA pill, thus, there is a potential for bias. Third, treatment adherence was not recorded in this study, which may alter the result. Fourth, the sample size in this study was small. The secondary outcomes e.g., spirometry and IOS parameters were not significantly different between groups and larger sample sizes should be investigated in the future to confirm or deny these findings. Lastly, our study included only patients with partially controlled asthma (GINA step 2 or 3) who were being treated by specialized chest physicians in a tertiary hospital. Therefore, the results of this study may not be generalizable to other GINA asthma classifications and other settings such as general practitioners or community hospitals.
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Author Contributions

Conceptualization, P.R., T.T., and W.C.; Methodology, P.R., T.T., W.C., and C.P.; Software: P.R. and W.C.; Validation, P.R., T.T., and W.C.; Formal Analysis, P.R. and W.C.; Investigation, P.R., T.T., W.C., N.P., and C.P.; Resources, P.R., T.T., and W.C.; Data Curation, P.R. and W.C.; Writing—Original Draft Preparation, P.R. and W.C.; Writing—Review and Editing, P.R., T.T., W.C., N.P., and C.P.; Visualization, T.T. and C.P.; Supervision, T.T. and C.P.; Project Administration, P.R., T.T., W.C., and C.P.; Funding Acquisition, P.R. and T.T. All authors have read and agreed to the published version of the manuscript.

Disclosure Statement

The authors declare that there is no conflict of interest in this work.

References