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To cite this article: Makoto Hoshino, Kenta Akitsu & Junichi Ohtawa (2018): Comparison between montelukast and tiotropium as add-on therapy to inhaled corticosteroids plus a long-acting β_2 -agonist in for patients with asthma, Journal of Asthma, DOI: [10.1080/02770903.2018.1514047](https://doi.org/10.1080/02770903.2018.1514047)

To link to this article: <https://doi.org/10.1080/02770903.2018.1514047>



Published online: 13 Sep 2018.



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Comparison between montelukast and tiotropium as add-on therapy to inhaled corticosteroids plus a long-acting β_2 -agonist in for patients with asthma

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ABSTRACT

Objective: Asthma often remains uncontrolled despite treatment with inhaled corticosteroids (ICS) alone or with ICS plus a long-acting β_2 -agonist (LABA). The recommended alternative is the addition of either montelukast or tiotropium. The aim of this study was to compare the effects of montelukast and tiotropium on airway inflammation and remodeling in persistent asthma. **Methods:** Eighty-seven patients with asthma were treated with budesonide and formoterol (640/18 μ g); then, the patients were randomly allocated to three groups to receive oral montelukast (10 mg/day), inhaled tiotropium (5 μ g/day), or no add-on to the maintenance therapy for 48 weeks. Fractional exhaled nitric oxide (FeNO) and pulmonary function were measured, and quantitative computed tomography was performed. **Results:** Compared to the maintenance therapy, add-on montelukast significantly decreased FeNO ($p < 0.05$) and improved airflow obstruction ($p < 0.05$), whereas airway dimensions remained unchanged. Changes in FeNO were significantly correlated with changes in FEV₁ ($r = -0.71$, $p < 0.001$). In contrast, the addition of tiotropium significantly decreased airway wall area corrected for body surface area (WA/BSA) ($p < 0.05$), decreased wall thickness (T/ $\sqrt$ BSA) ($p < 0.05$) and improved airflow obstruction ($p < 0.05$) with no change in FeNO. Changes in WA/BSA and T/ $\sqrt$ BSA were significantly correlated with the change in percentage predicted FEV₁ ($r = -0.84$, $p < 0.001$ and $r = -0.59$, $p < 0.01$, respectively). **Conclusions:** Adding either montelukast or tiotropium to ICS/LABA may provide additive benefits with respect to the pulmonary function and airway inflammation or remodeling in patients with asthma.

ARTICLE HISTORY

Received 19 April 2018
Revised 13 August 2018
Accepted 15 August 2018

KEYWORDS

Asthma; inflammation; montelukast; remodeling; tiotropium

Introduction

Asthma is a condition characterized by chronic airway inflammation and intermittent symptoms; it affects 300 million people worldwide [1]. The Global Initiative for Asthma (GINA) recommends the use of inhaled corticosteroids (ICS) in combination with a long-acting β_2 -agonist (LABA) for patients with asthma that is inadequately controlled by low-to-medium dose ICS monotherapy; however, at least 40% of patients still experience asthma symptoms while on this regimen [2–4]. Therefore, the addition of other controller medications—such as leukotriene modifiers, sustained-release theophylline, or long-acting muscarinic antagonists (LAMA)—is often required.

Montelukast is an orally administered leukotriene receptor antagonist (LTRA); adding LTRA to ICS or ICS plus a LABA has been demonstrated to improve

asthma control and pulmonary function in clinical trials [5–8]. Tiotropium, a LAMA, has been investigated as an add-on treatment to a maintenance therapy of ICS plus a LABA in patients with symptomatic moderate-to-severe asthma [9–11]. A review of previous studies showed that no data were available to show a difference in response between montelukast and tiotropium as add-on therapies in patients with asthma.

The present study was performed to provide a head-to-head comparison of montelukast to tiotropium as third-line medications commonly used in clinical settings. Different clinical measurements have been used to study the pathophysiology of asthma. Measurement of fractional exhaled nitric oxide (FeNO) has been used to assess airway inflammation and is preferred over other tests due to its noninvasiveness, simplicity, and reproducibility [12]. Airway wall thickening is a prominent feature of airway

remodeling, and it has been evaluated noninvasively using computed tomography (CT) [13]. The aim of the present study was to compare the effects of montelukast and those of tiotropium on airway inflammation and airway remodeling in patients with persistent asthma who were already being treated with ICS plus a LABA.

Methods

Study design

This was a randomized, open-label, three-arm clinical trial (Figure 1). All patients provided written, informed consent, and the study protocol was approved by our hospital ethics committee. This trial was registered with the University Hospital Medical Information Network (<http://www.umin.ac.jp>, UMIN000019042). Randomization was performed using a pseudo-random number generator, a supplied seed number, and a fixed-block sequence; the block size was six. During a 4-week run-in period, all patients were given budesonide/formoterol (AstraZeneca, Lund, Sweden) (160/4.5 μ g) 2 inhalations twice daily. At the end of the run-in period, the patients were allocated to receive treatment with one of the following for 48 weeks: oral montelukast (MSD, Kenilworth, NJ, USA) (10 mg) once daily; inhaled tiotropium (Respimat® SoftMist inhaler, Boehringer Ingelheim, Ingelheim am Rhein, Germany) (5 μ g) once daily; or no add on to the maintenance treatment (budesonide/formoterol). A short-acting β_2 -agonist was provided as a rescue medication for use when required. After screening, which was conducted before the 4-week run-in period, subsequent clinical visits were scheduled once every 4 weeks during the 48-week treatment period. Spirometry, FeNO measurement, CT examination, blood tests, evaluation of

the frequency of exacerbations, and assessment of a quality of life using a questionnaire were conducted during the run-in period and on week 48.

Subjects

Male and female outpatients who had a documented history of asthma of more than 3 months and were symptomatic at the time of screening were enrolled. Asthma was diagnosed based a clear history of relevant symptoms and documented reversible airway obstruction ($>12\%$ improvement in forced expiratory volume in 1 s (FEV₁) after inhalation of a short-acting β_2 -agonist). In addition, patients had to have been on maintenance therapy with ICS plus a LABA for 4 or more weeks prior to the screening and an FEV₁ $>60\%$ of the predicted normal value. Eligible patients were nonsmokers or ex-smokers with less than 5 packs-years who had stopped smoking at least 1 year before enrollment. Key exclusion criteria included a diagnosis of chronic obstructive pulmonary disease or any respiratory disease other than asthma, glaucoma, prostatic hyperplasia or respiratory tract infection in the 2 weeks prior to screening.

Pulmonary function

Spirometry was performed using a computerized system (Fukuda Denshi, Tokyo, Japan). The predicted values of forced vital capacity (FVC) and FEV₁ for a Japanese population were calculated using the formula proposed by the Japanese Respiratory Society [14].

FeNO

FeNO was measured using a portable NO analyzer (NioxMino, Aerocrine, Solna, Sweden), which

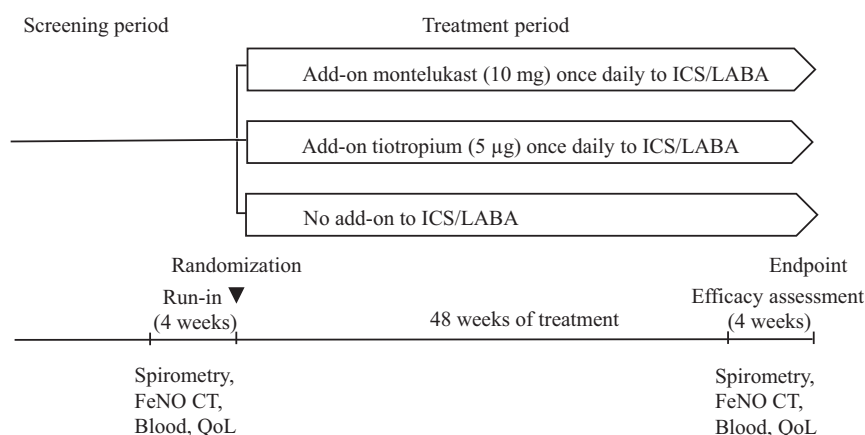


Figure 1. Study design.

provides measurements at an exhalation flow rate of 50 ml/s.

CT measurements

All subjects were scanned using a 64-multislice scanner (Aquilion-64, Toshiba Medical, Tokyo, Japan) at full inspiration as described previously [15,16]. The scans parameters were as follows: 120 kV, 200 mA, and a slice thickness of 1 mm. The full-width at half-maximum principle [17] was applied to determine the following airway parameters: luminal area (A_i), total area of the airway (A_o), wall area ($WA = A_o - A_i$), absolute wall thickness (T), and percentage of the wall area ($WA/A_o = WA/A_o \times 100$) at the right upper lobe apical segmental bronchus (RB1). Because airway size may be affected by body size, A_i , WA , and T were normalized to the body surface area (BSA). Details of data reproducibility are described elsewhere [15].

Eosinophils count and immunoglobulin E measurements

Blood eosinophil count was measured using hemocytometry. Total and allergen-specific serum immunoglobulin E (IgE) levels were measured using a radioallergosorbent fluoroenzyme immunoassay test (Phadia, Uppsala, Sweden). Subjects who had at least one allergen-specific IgE antibody were regarded as atopic.

Asthma exacerbations

Asthma exacerbation was defined as the presence of at least one of the following events: oral corticosteroid treatment, an unscheduled visit to the doctor's office, or hospitalization because of worsening asthma.

Quality of life

Asthma control was assessed using the Asthma Quality of Life Questionnaire (AQLQ), which contains 32 items that cover four domains (symptoms, activities, emotions, and environment) using a 7-point scale [18]. Rhinitis was diagnosed based on symptoms (e.g. sneezing, rhinorrhea, nasal obstruction and itching). Patients with rhinitis symptoms at inclusion were asked to evaluate their status as either "improved," "unchanged," or "worse" at the end of the study.

Outcome measurements

The primary objective of the study was to evaluate the effects of montelukast and tiotropium on airway inflammation and airway dimensions. The secondary outcomes evaluated were pulmonary function, blood test results, and symptoms.

Statistical analysis

Data are presented as the mean (standard deviation [SD]) or median (interquartile range [IQR]). The paired t -tests or the Wilcoxon signed-rank tests were used to compare variables before and after treatment. Comparisons between the two groups were performed using unpaired t -tests. Comparisons of multiple groups were performed using analysis of variance (ANOVA) with the Bonferroni correction. Relationships between parameters were assessed using the Pearson correlation coefficients. A p value <0.05 was considered significant. All data were analyzed using StatView software (SAS Institute, Cary, NC, USA).

Results

Subjects

A total of 122 patients were screened, and 102 patients were randomized into treatment. Of the latter, 87 patients completed the study. The characteristics of the patients are shown in Table 1. Patient demographic and baseline characteristics were similar among the three groups.

Primary endpoints

The addition of montelukast to ICS/LABA significantly decreased FeNO [mean (SD) 52.0 ± 6.8 at baseline to 44.6 ± 6.3 ppb at the end of treatment, $p < 0.05$]. No significant changes in WA/BSA , $T/\sqrt{BSA}$, WA/A_o , or A_i/BSA were observed in patients treated with add-on montelukast [median (IQR) 16.7 (13.0–20.1) to 16.4 mm^2/m^2 (13.4–19.4), $p = 0.411$; 1.08 (0.86–1.26) to 1.05 mm/m (0.89–1.21), $p = 0.141$; 68.6 (61.2–71.4) to 65.5% (60.6–70.4), $p = 0.456$; 7.3 (3.9–9.1) to 7.4 mm^2/m^2 (4.2–9.3), $p = 0.478$, respectively]. There was a significant difference in FeNO between patients treated with montelukast plus ICS/LABA and those treated with ICS/LABA ($p < 0.05$, Table 2). There was no significant change in FeNO in patients treated with add-on tiotropium [mean (SD) 49.5 ± 5.0 to 46.2 ± 5.3 ppb, $p = 0.104$]. The addition of

Table 1. Characteristics of asthmatic patients.

	Montelukast + ICS/LABA (n = 28)	Tiotropium + ICS/LABA (n = 29)	ICS/LABA (n = 30)	p-value
Age (yr)	51 (12)	55 (14)	54 (16)	0.21
Male/female	12/16	13/16	12/18	0.46
Body mass index (kg/m ²)	24.5 (3.4)	25.2 (7.0)	24.2 (5.1)	0.24
Asthma duration (yr)	14 (14)	14 (12)	17 (17)	0.36
Atopy (n)	18	20	21	0.14
Allergic rhinitis (n)	17	18	17	0.29
Allergic dermatitis (n)	2	3	5	0.08
Serum IgE (IU/ml)	406.8 (415.8)	541.1 (553.6)	523.1 (665.2)	0.21
Pulmonary function				
FVC (% predicted)	94.6 (15.4)	95.0 (19.5)	97.1 (17.4)	0.13
FEV ₁ (% predicted)	70.0 (9.7)	72.6 (10.0)	71.5 (10.1)	0.15
FEV ₁ /FVC (%)	71.8 (12.0)	72.4 (12.3)	75.7 (9.2)	0.18
FeNO (ppb)	52.0 (6.8)	49.5 (5.0)	49.0 (4.0)	0.06
CT scan measurement				
WA/BSA (mm ² /m ²)	16.7 (13.0–20.1)	16.6 (13.4–19.2)	16.3 (13.1–19.5)	0.36
T/ $\sqrt{BSA}$ (mm/m)	1.08 (0.86–1.26)	1.09 (0.94–1.24)	1.04 (0.91–1.11)	0.48
WA/Ao (%)	68.6 (61.2–71.4)	69.1(63.6–74.4)	69.9 (64.1–74.9)	0.08
Ai/BSA (mm ² /m ²)	7.3 (3.9–9.1)	7.5 (4.6–8.8)	6.3 (4.5–7.5)	0.06
Blood eosinophil (/ μ l)	385.8 (272.8)	367.1 (290.5)	330.7 (236.0)	0.19
Exacerbation (% of patients) [†]	34	36	37	0.21
AQLQ score				
Symptoms	5.6 (1.0)	5.5 (1.1)	5.8 (0.9)	0.13
Activities	5.6 (0.9)	5.6 (1.0)	5.9 (1.0)	0.27
Emotions	5.4 (1.0)	5.3 (1.1)	5.9 (1.1)	0.10
Environment	5.7 (1.1)	5.8 (1.2)	5.9 (1.2)	0.41

Data are presented as mean (SD) or median (IQR).

ICS: inhaled corticosteroid; LABA: long-acting β_2 -agonist; IgE: immunoglobulin E; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; FeNO: fractional exhaled nitric oxide; WA: airway wall area; T: absolute wall thickness; Ao: total area of the airway; Ai: luminal area; BSA: body surface area; AQLQ: asthma quality of life questionnaire, four domains (symptoms, activities, emotions, and environment) using a 7-point scale.

[†]Asthma exacerbations in the previous year.

Table 2. Changes in parameters from baseline and efficacy after treatment with add-on montelukast, add-on tiotropium or ICS/LABA alone.

Variable	Montelukast + ICS/LABA	Tiotropium + ICS/LABA	ICS/LABA	p value comparing		
				Montelukast + ICS/LABA vs ICS/LABA	Tiotropium + ICS/LABA vs ICS/LABA	Montelukast + ICS/LABA vs Tiotropium + ICS/LABA
Pulmonary function						
FVC (mL)	111.6 (15.4)	155.1 (15.3)*	47.8 (19.3)	0.220	0.057	0.370
FVC (% predicted)	6.0 (3.0)	8.6 (2.9)	2.6 (3.4)	0.386	0.190	0.417
FEV ₁ (mL)	98.0 (15.5)*	114.4 (14.9)*	24.6 (19.8)	0.047	0.035	0.324
FEV ₁ (% predicted)	5.4 (3.7)*	8.4 (3.4) [†]	0.6 (3.3)	0.028	0.006	0.232
FEV ₁ /FVC (%)	1.2 (2.8)	1.8 (2.6)	0.4 (2.6)	0.266	0.194	0.360
FeNO (ppb)	−5.6 (4.9)*	−2.8 (3.8)	−1.6 (2.4)	0.044	0.103	0.071
CT scan measurement						
WA/BSA (mm ² /m ²)	−0.4 (−0.1, −1.6)	−1.1 (−0.2, −1.9)*	−0.4 (−0.1, −1.3)	0.237	0.037	0.082
T/ $\sqrt{BSA}$ (mm/m)	−0.03 (0, −0.09)	−0.10 (0, −0.16) [†]	−0.01 (0, −0.12)	0.102	0.040	0.068
WA/Ao (%)	−0.7 (1.5, −3.5)	−1.8 (0.1, −4.6)	−0.5 (1.6, −3.5)	0.444	0.065	0.085
Ai/BSA (mm ² /m ²)	0.3 (0.2, 0.9)	0.6 (0.4, 1.7)	0.2 (0.1, 0.8)	0.213	0.167	0.216
Blood eosinophil (/ μ l)	−116.2 (241.5) [†]	−65.7 (236.1)	−34.0 (244.6)	0.009	0.125	0.065
AQLQ						
Symptoms	0.5 (1.0)*	0.5 (1.0)*	0.2 (0.9)	0.030	0.037	0.229
Activities	0.2 (0.5)	0.2 (0.5)	0.2 (1.0)	0.096	0.137	0.070
Emotions	0.2 (1.0)	0.3 (0.9)*	0.2 (1.2)	0.186	0.110	0.268
Environment	0.3 (0.8)*	0.3 (1.0)	0.1 (1.0)	0.394	0.400	0.406

Data are presented as means (SD) or medians (IQR). ICS: inhaled corticosteroid; LABA: long-acting β_2 -agonist; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; FeNO: fractional exhaled nitric oxide; WA: airway wall area; T: absolute wall thickness; Ao: total area of the airway; Ai: luminal area; BSA: body surface area; AQLQ: asthma quality of life questionnaire, four domains (symptoms, activities, emotions, and environment) using a 7-point scale.

* $p < 0.05$.

[†] $p < 0.01$: compared with baseline, for within-group comparisons.

tiotropium to ICS/LABA significantly decreased WA/BSA and T/ $\sqrt{BSA}$ [median (IQR) 16.6 (13.4–19.2) to 15.5 mm²/m² (12.2–17.0), $p < 0.05$; 1.09 (0.94–1.24) to

0.99 mm/m (0.85–1.16), $p < 0.05$], but not WA/Ao or Ai/BSA [median (IQR) 69.1(63.6–74.4) to 67.6% (61.6–73.0), $p = 0.188$; 7.5 (4.6–8.8) to 7.9 mm²/m²

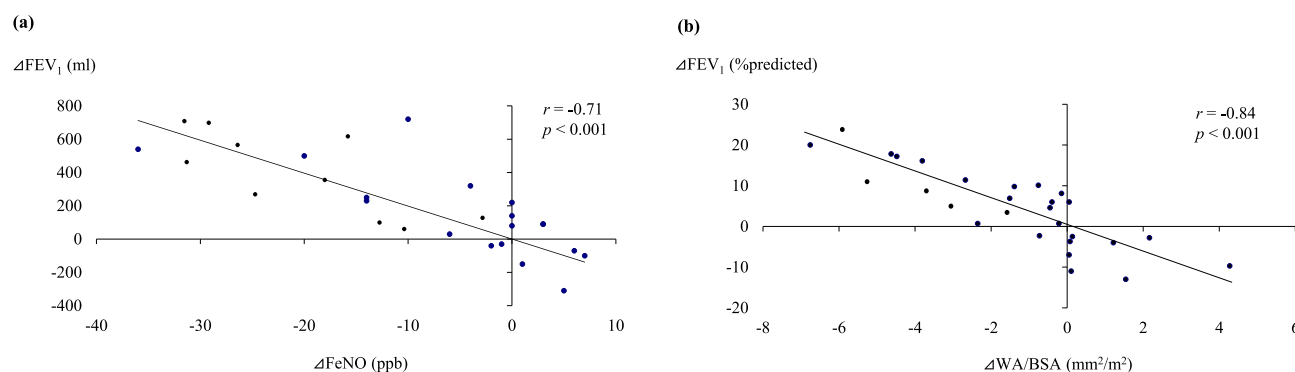


Figure 2. Relationship between changes in (a) fractional exhaled nitric oxide (FeNO) and forced expiratory volume in 1 s (FEV₁) before and after add-on treatment with montelukast and (b) wall area normalized to body surface area (WA/BSA) and FEV₁% predicted before and after add-on treatment with tiotropium.

(4.9–9.4), $p = 0.104$]. The difference in the changes in WA/BSA and $T/\sqrt{BSA}$ between patients treated with tiotropium plus ICS/LABA and those treated with ICS/LABA was statistically significant (each $p < 0.05$, Table 2). No significant changes in FeNO or airway dimensions were observed in patients on maintenance therapy. No statistically significant difference was observed between the montelukast and the tiotropium treatment group with respect to improvement in FeNO or airway wall thickness.

Secondary endpoints

Treatment with montelukast resulted in significant increases in FEV₁ ($p < 0.05$) and FEV₁% predicted ($p < 0.05$). There were also significant increases in FVC ($p < 0.05$), FEV₁ ($p < 0.05$) and FEV₁% predicted ($p < 0.01$) after treatment with tiotropium. Differences in spirometric parameters between patients treated with montelukast plus ICS/LABA and those treated with ICS/LABA and between patients treated with tiotropium plus ICS/LABA and those treated with ICS/LABA were significant (Table 2). The changes in FeNO were correlated with the changes in FEV₁ ($r = -0.71$, $p < 0.001$) (Figure 2a) and FEV₁% predicted ($r = -0.60$, $p < 0.01$) in the montelukast group. The changes in FEV₁ were correlated with the changes in WA/BSA ($r = -0.82$, $p < 0.001$) and $T/\sqrt{BSA}$ ($r = -0.56$, $p < 0.01$). Furthermore, the changes in FEV₁% predicted were correlated with the changes in WA/BSA ($r = -0.84$, $p < 0.001$) (Figure 2b) and $T/\sqrt{BSA}$ ($r = -0.59$, $p < 0.01$) in the tiotropium group. The addition of montelukast significantly reduced the blood eosinophil count compared with maintenance therapy [mean (SD) $116.2 \pm 241.5/\mu\text{l}$ versus $34.0 \pm 244.6/\mu\text{l}$, $p < 0.01$] (Table 2). The percentage of patients with asthma exacerbations in both the montelukast- and tiotropium-added groups decreased

significantly, from 34 to 20% and 36 to 18%, respectively (each, $p < 0.05$), whereas maintenance therapy group exhibited no change in exacerbations. Between-group comparisons indicated significantly greater improvements in the symptom score in the montelukast and the tiotropium group than in the ICS/LABA alone group (Table 2).

Moreover, 70% of patients with both asthma and rhinitis ($n = 11$) in the montelukast group reported improvement in nasal symptoms. There were no changes in rhinitis symptoms in the tiotropium group. The objective measurements—including the change in pulmonary function, blood eosinophil count, AQLQ, and exacerbation rates—were not significantly different between the montelukast and tiotropium treatment groups.

Safety

Montelukast and tiotropium were well tolerated, and there were no serious drug-related adverse events. The most frequently reported adverse events associated with montelukast, grouped by system organ class, were infections, gastrointestinal disorders, and skin disorders. The most frequently reported adverse events associated with tiotropium were oral thrush, sore throat, cough and laryngeal discomfort. There were no patients who discontinued treatment because of adverse events.

Discussion

Currently, it is not yet known from clinical data whether the additive benefits seen with the use of ICS plus a LABA are a result of their bronchodilatory actions or some poorly understood anti-inflammatory or remodeling inhibition mechanism. We investigated the physiological and airway inflammation and

remodeling effects of add-on montelukast and tiotropium in patients with symptomatic asthma. When montelukast was added to the maintenance therapy of ICS/LABA, it significantly reduced the eosinophilic inflammation. This was associated with an increase in FEV₁; however, airway wall thickness remained unchanged. FeNO has been shown to serve as a surrogate marker of airway inflammation in asthma. Steroid therapy is associated with a reduction in FeNO and improvement in FEV₁ [19]. Therefore, the improvement of pulmonary function after add-on montelukast in the current study may reflect the reduced airway inflammation. On the other hand, the addition of tiotropium decreased airway wall thickness significantly and improved pulmonary function without demonstrating any anti-inflammatory effects. Moreover, the changes in airway geometry were significantly associated with improvements in airflow limitation. Airway wall thickness contributes to the degree of airflow obstruction in asthma. We have previously reported that budesonide/formoterol combination is more effective than budesonide alone in reducing airway wall thickness, and this effect is associated with an increase in FEV₁ [16]. The addition of tiotropium improved airflow limitation probably through modifying the airway remodeling. To the best of our knowledge, this is the first study comparing the efficacy of treatment with montelukast to that of treatment with tiotropium in patients with asthma.

Cysteinyl leukotrienes (LT) induce many pathologic changes in the lung, including airflow obstruction, increased mucous secretion, and inflammatory cell infiltration [20]. Several studies have demonstrated the ability of LTRA to reduce airway inflammation [21], reduce asthmatic symptoms, and improve lung function [22]. These observations may be due to the anti-inflammatory effects of montelukast based on the reduction of several indices of inflammation—including the eosinophil counts in peripheral blood and sputum [23], bronchial mucosa [24] and eosinophilic cationic protein in nasal washes [25]—in patients with asthma. A number of studies evaluating induced sputum, bronchoalveolar lavages (BAL), and bronchial biopsies have shown that FeNO reflects eosinophilic inflammation [26]. It has been demonstrated that FeNO is higher in patients with asthma than in healthy subjects [27]; however, high levels of FeNO have been reported in some patients with asthma despite the use of oral or high-dose inhaled corticosteroids [28]. These findings suggest that some patients with asthma may be partially insensitive to the usual doses of steroid; thus, such doses cannot fully control

the asthmatic inflammation. LTE₄ concentration in BAL is not affected by high doses of oral corticosteroids, and ICS have no effect on urinary LTE₄ excretion after an allergen challenge [29,30]. In the present study, the addition of montelukast to a regular treatment with ICS/LABA in patients with asthma resulted in a significant reduction in FeNO; however, no change in FeNO was observed in the maintenance therapy group. This suggests that montelukast may be a useful third-line therapy that can help to control airway inflammation. Furthermore, the reduction in FeNO was associated with significant changes in FEV₁. Several studies have shown the effectiveness of adding montelukast to ICS or ICS plus LABA in improving asthma symptoms and lung function [6,31–34]. Currie et al. have shown that montelukast conferred additional benefits with respect to surrogate inflammatory markers when added to fluticasone/salmeterol therapy [35]; montelukast may have additional benefits in asthma control through targeting an inflammatory pathway distinct from that of steroids.

In contrast, the addition of tiotropium had no effect on FeNO. Another study, which had similar findings to ours, suggested that adding tiotropium did not change the sputum eosinophil count or FeNO in patients with moderately severe asthma [9]. However, in short-term animal studies focusing on allergic asthma, it has been shown that tiotropium has anti-inflammatory effects [36,37]. The discrepancy between these studies suggests there is need to explore the potential of tiotropium to improve inflammatory parameters, including not only eosinophil count but also levels of Th2 cytokines in patients with asthma.

Airway structural changes—such as subepithelial fibrosis, increased smooth muscle mass, and goblet cell hyperplasia—contribute to airway remodeling. Although the components of the airway wall—including the subepithelium, mucosa and smooth muscle—cannot be individually assessed using CT, imaging techniques make it possible to measure the overall airway wall thickness. Based on the results of CT imaging, there was no significant improvement in the indices of airway geometry following the addition of montelukast. The irreversible components of airway remodeling in symptomatic asthma may be responsible for this effect. Our results are consistent with the previously observed lack of effect of montelukast on reticular basement thickness in a human bronchial biopsy study [24]. However, a previous study in ovalbumin-sensitized and challenged mice showed the preventive effect of montelukast on airway remodeling, which supports the hypothesis that montelukast

can potentially affect airway remodeling in the short term [38]. Further studies to evaluate the effect of montelukast on airway remodeling in patients with asthma are warranted.

Tiotropium inhibits several aspects of airway remodeling, including mucin expression, goblet cell metaplasia, smooth muscle hypertrophy, and airway fibrosis [36,37,39–41]. Muscarinic receptors regulate proliferation of airway smooth muscle cells [42], proliferation of fibroblasts, and deposition of extracellular matrix deposition [43,44]. *In vitro*, the anticholinergic medication glycopyrrolate has been shown to act synergistically with budesonide in inhibiting TNF- α release from isolated monocytes, which indicates that the combination of anticholinergics and corticosteroids may be more effective than monotherapy [45]. Recently, repeated methacholine challenges have been shown to induce airway remodeling without airway eosinophilic recruitment in patients with asthma [46]. Bronchoconstriction is effectively targeted by tiotropium because mechanical forces by themselves may be an important driver of airway remodeling. In view of the abovementioned beneficial effects of tiotropium and ICS/LABA, this combination therapy might have additive protective effects on airway remodeling.

Montelukast and tiotropium were equally effective in controlling asthma symptoms, improving lung function, and reducing rates of exacerbation. Up to 80% of patients with asthma have rhinitis, and patients with comorbid asthma and rhinitis have worse asthma control than those without the comorbid conditions [47]. Consistent with a previous report [48], we observed a significant improvement in rhinitis after the addition of montelukast in the patients who had both asthma and rhinitis. With respect to anti-inflammatory effects, ICS/LABA plus montelukast may be superior to ICS/LABA. Additionally, with respect to anti-remodeling effects, ICS/LABA plus tiotropium may be more useful than ICS/LABA alone. If airway inflammation contributes more to the pathogenesis of asthma than airway remodeling, it may be better to select montelukast as a third line therapy, conversely, if the opposite is true, tiotropium would be a better third-line medication.

There were some limitations in the present study. First, this study did not include a placebo arm. A study with a placebo arm is desirable in any clinical trial. Instead of a placebo, ICS/LABA maintenance therapy was used as a positive control to compare the two other regimens. Other long-term studies of asthma therapy have included a placebo group that enrolled patients with mild asthma [49]. It is also

important to determine the therapeutic effectiveness of treatment options in real-life populations, settings, and durations in order to complement the clinical data. Second, we evaluated only a small number of patients, which could potentially affect the accuracy of the outcomes. To confirm the present findings, further studies with larger sample sizes should be performed. Third, only one segmental bronchus was assessed. The airway geometry of patients with asthma has been found to be narrowed heterogeneously [50]. Nevertheless, recent studies suggest that the dimensions of RB1 are closely related to dimensions of other bronchi [15,51,52]. Therefore, RB1 dimensions serve as a good surrogate for airway wall remodeling in asthma.

Conclusions

Triple therapy, consisting of montelukast or tiotropium added to ICS/LABA, is effective in improving inflammation or remodeling, airflow limitation, and symptoms in patients with persistent asthma. Measurements of FeNO and those of airway wall thickness by using CT appear to be valuable tools in the noninvasive evaluation of inflammation and remodeling.

Acknowledgements

The authors would like to thank all of the staff members in the Department of Laboratory Medicine at Atami Hospital International University of Health and Welfare.

Disclosure statement

All authors have no conflicts of interest to declare.

Funding

We have no funding sources.

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