A Single Institution Retrospective Study of the Clinical Efficacy of Tiotropium Respimat in Never-Smoking Elderly Asthmatics with Irreversible Airflow Limitation

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Key words

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ABSTRACT

Objective In Japan, most asthma deaths occur among the elderly. We should improve the control of asthma in elderly patients to reduce the number of deaths due to asthma. This retrospective study aimed to evaluate the efficacy of tiotropium Respimat® (Tio-Res) in symptomatic, never-smoking, elderly asthmatics with irreversible airflow limitation despite the use of high-dose inhaled corticosteroids (ICS) plus long-acting β_2-adrenoceptor agonists (LABA).

Methods The Asthma Control Test™ (ACT), pulmonary function tests, morning and evening peak flow (mPEF, ePEF, respectively, evaluated with an ASSESS® peak flow meter), and respiratory impedance (assessed with MostGraph®) were measured before and after a minimum of one year of Tio-Res 5 µg/day administration. Sixteen symptomatic, never-smoking asthmatics, aged 75 or over with irreversible airflow limitation despite the use of high-dose ICS plus LABA, were analyzed.

Results All patients were female (mean age, 81.6 years). Tio-Res led to statistically significant improvements in the total ACT score (19.9 to 23.6), FVC and FEV_1 (1.97 to 2.14 L and 1.13 to 1.23 L, respectively), and mPEF and ePEF (229.9 to 253.8 L/min and 259.8 to 277.4 L/min, respectively). Tio-Res also resulted in statistically significant improvements in respiratory resistance at 5 Hz (R5), respiratory resistance at 20 Hz (R20), R5-R20, low-frequency reactant indices at 5 Hz (X5), resonant frequency (Fres) and low-frequency reactance area (ALX).

Conclusions Our retrospective study suggests that Tio-Res improves symptoms, pulmonary function, and respiratory impedance in symptomatic asthmatics aged 75 or over with irreversible airflow limitation despite the use of high-dose ICS plus LABA.

Abbreviations

ACT	Asthma Control Test
ALX	low-frequency reactance area
BDP	beclometasone dipropionate
BMI	body mass index
COPD	chronic obstructive pulmonary disease
DLco	diffusing capacity of lung for carbon monoxide
DLco/VA	diffusing capacity of lung for carbon monoxide divided by the alveolar volume
FEV_1	forced expiratory volume in 1 s
Fres	resonant frequency

FVC	forced vital capacity
FOT	the forced oscillation technique
HRCT	high-resolution computed tomography
Fres	resonant frequency
IC	inspiratory capacity
ICS	inhaled corticosteroid
LABA	long-acting β2-adrenoceptor agonist
LAMA	long-acting muscarinic antagonists
LTRA	leukotriene receptor antagonists
MEF_{25-75}	maximal expiratory flow between 25 % and 75 % of. FVC
MEF_{50}	maximal expiratory flow at 50 % of. FVC
MEF_{75}	maximal expiratory flow at 75 % of FVC
PEF	peak flow
R5	respiratory resistance at 5 Hz
R20	respiratory resistance at 20 Hz
Rrs	respiratory resistance
Tio	tiotropium
Tio-Hand	tiotropium Handihaler®
Tio-Res	tiotropium Respimat®
X5	respiratory system reactance at 5 Hz
Xrs	respiratory system reactance

Introduction

In clinical settings, inhaled corticosteroid (ICS) plus long-acting β_2-adrenoceptor agonist (LABA) combination therapy is one of the most common treatments for bronchial asthma and is often combined with other treatments, such as leukotriene receptor antagonists (LTRA) or sustained-release theophylline. However, insufficiently controlled asthma continues to exist, despite the use of high-dose ICS plus LABA [1]. In Japan, most asthma deaths occur among the elderly [2, 3]; therefore, we should improve the control of asthma in elderly patients to reduce the number of deaths due to asthma. It has previously been reported that tiotropium (Tio) has beneficial effects in asthma when added to ICS monotherapy [4, 5] or to combination therapy consisting of ICS and LABA [6, 7]. However, data concerning the efficacy of Tio in asthmatic patients over 75 years old are scarce.

Irreversible airflow limitation can occur in asthmatic patients who have never smoked, and persistent irreversible airflow limitation is one of the most important characteristics of patients with frequent asthma exacerbations [8]. In elderly patients with asthma, airway remodeling induced by long-standing asthma [9] or age-related pathological changes of the respiratory system [10] can cause irreversible airflow limitation. A recent study indicated that bronchoconstriction itself could cause airway remodeling in patients with asthma [11].

To our knowledge, data regarding the medicinal effect of tiotropium via the Respimat Soft Mist inhaler® (Boehringer Ingelheim, Ingelheim am Rhein, Germany) (Tio-Res) in never-smoking elderly asthmatics with chronic airflow limitation are scarce. Here, we retrospectively studied the efficacy of Tio-Res on symptoms, lung function, and respiratory impedance in symptomatic, never-smoking, elderly (aged 75 years or older) asthmatics with chronic airflow limitation despite the use of high-dose inhaled ICS and LABA.

Patients and Methods

This retrospective, observational study was performed at the Department of Respiratory Medicine, Kanazawa University Hospital. The study included outpatients, aged 75 years or over, who had performed the Asthma Control Test (ACT), pulmonary function tests, and forced oscillation technique (FOT) before and after a minimum of one year of Tio-Res administration. This study was approved by the Medical Ethics Committee of Kanazawa University Hospital (registration number 2016-192) and carried out by the opt-out method of poster information. All patients satisfied the 2017 Japanese guidelines for adult asthma [2], including repetitive symptoms, such as paroxysmal dyspnea, wheezing, and chest tightness, reversible airflow limitation, airway hyperresponsiveness documented on at least one previous pulmonary function study, and exclusion of other cardiopulmonary diseases. Despite the use of high-dose ICS plus LABA, all of the participants were symptomatic and had airflow limitation as demonstrated by a baseline ACT [12] score under 24 and forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) < 70 %. Patients with any of the following were excluded from the study: a history of active smoking, a requirement for supplemental oxygen, an area of low attenuation on chest high-resolution computed tomography (HRCT), % diffusing capacity for carbon monoxide (%DLco) < 80 %, %DLco/alveolar volume (VA) < 80 %, known prostatic hypertrophy, or angle-closure glaucoma.

Tio-Res, 5 µg, was added to each patient's asthma control medication package and was administered once every morning. The ACT score, pulmonary function tests, monthly mean morning and evening peak flow (mPEF and ePEF, respectively), and respiratory impedance were assessed at baseline and after at least one year of add-on Tio-Res therapy. Pulmonary function tests and respiratory impedance following Tio-Res therapy were measured 3 h after inhalation of Tio-Res. Respiratory impedance parameters were used in the inspiratory phase. Pulmonary function and respiratory impedance were measured with CHESTAC-9800 and MostGraph-01, respectively (both, Chest Co., Tokyo, Japan). PEF was measured with the ASSESS peak flow meter (Philips Co., Amsterdam, Netherlands). Predicted values for FVC and FEV_1 for Japanese patients were calculated by the formula proposed by the Japanese Respiratory Society [13].

Statistical analysis

Data values were expressed as the mean ± standard deviation (SD). The Wilcoxon test was used to compare the ACT score, pulmonary function parameters, respiratory impedance, and PEF. The degree of association between two variables was determined using the Spearman rank correlation coefficient. All comparisons were two-tailed, and probability values < 0.05 were considered significant. Statistical analyses were performed with SPSS Statistics 23 (Japan IBM Co., Tokyo, Japan).

Results

In total, 16 patients with a mean age of 81.6 years (median 80.0, range 77–86) were recruited for the study. All patients were female. The baseline characteristics of the study participants are summarized in ▶ **Table 1**. The mean daily dose of ICS in the equivalent dose of beclometasone dipropionate (BDP) was 778.3 µg/day at baseline.

The mean FVC, FEV_1, and FEV_1/FVC were 1.97 L (%pred, 91.2 %), 1.13 L (%pred, 68.9 %), and 57.7 %, respectively. The mean MEF_{25-75}, MEF_{50} and MEF_{75} were 0.42 L/sec (%pred, 21.8 %), 0.62 L/sec (%pred, 26.5 %), and 0.14 L/sec (%pred, 22.7 %), respectively. The mean DLco and DLco/VA were 15.64 mL/min/mmHg (%pred, 90.8 %) and 4.94 mL/min/mmHg/L (%pred, 103.9 %), respectively. Leukotriene receptor antagonists were administered in 8 of 16 patients (50 %). Once-daily Tio-Res 5 µg produced significant improvements in the total ACT score (19.9 to 23.6, $p < 0.05$), shown in ▶ **Fig. 1**, and the FVC (1.97 to 2.14 L, $p < 0.05$), FEV_1 (1.13 L to 1.23 L, $p < 0.01$), MEF_{25-75} (0.42 to 0.49 L/sec, $p < 0.05$), mPEF (229.9 to 253.8 L/min, $p < 0.01$), and ePEF (259.8 to 277.4 L/min, $p < 0.05$), shown in ▶ **Table 2**. Tio-Res also resulted in significant improvements in inspiratory phase respiratory resistance at 5 Hz (R5), respiratory resistance at 20 Hz (R20), R5-R20, low frequency reactant indices at 5 Hz (X5), resonant frequency (Fres) and low-frequency reactance area (ALX) ($p < 0.05$ for all, shown in ▶ **Table 2**). Tio-Res dramatically improved the respiratory impedance (▶ **Table 2**). Several measurements were illustrated as box-and-whisker plot (▶ **Fig. 2**). Significant correlation between inspiratory phase R5-R20 or reactance (Xrs) values and FEV_1 or %pred FEV_1 were observed (▶ **Table 3**).

Discussion

Our retrospective study suggested that Tio-Res improved asthma symptoms, pulmonary function, and respiratory impedance in symptomatic, elderly asthmatics, aged 75 years or over with irreversible airflow limitation despite the use of high-dose ICS plus LABA. In 2012, a randomized double-blind placebo-controlled study evaluated the add-on effect of long-term (48 weeks) treatment with Tio-Res 5 µg/day in patients with symptomatic asthma despite using moderate to high doses of ICS (budesonide equivalent daily dose ≧800 µg/day) plus LABA. The addition of Tio-Res significantly improved FEV_1 and morning and evening PEF and decreased the rate of severe exacerbations [6]. Subgroup analyses of this study showed that Tio-Res was effective independent of age (18-40, 40-60 and 60-75 years), %pred FEV1 (< 60, 60- < 80, and ≧80 %) or smoking status [14]. The results of our study are consistent with these findings. Furthermore, our study showed that Tio-Res was effective in elderly patients aged 75 years or over. To our knowledge, our study is the first to evaluate the efficacy of Tio-Res in that age group and to show that even in very elderly asthmatic patients, irreversible airflow limitation may be a 'treatable trait'. In Japan, patients aged 75 years or over accounted for 79.6 % of 1,454 asthma deaths in 2016 [3]. Irreversible airflow limitation is very important because reduced lung function is a risk factor for adverse asthma outcomes [15–17], and our results may suggest that Tio-Res is beneficial for preventing asthma deaths. We should not overlook the abnormal irreversible airflow limitation as normal aging change, though the FEV_1/FVC ratio decreases with age.

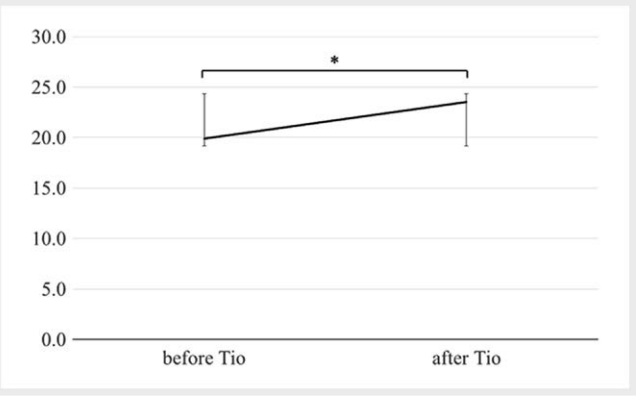
Although we could not completely exclude the influence of passive cigarette smoke or air pollution on irreversible airflow limitation, we excluded from the current study any patients showing the features of COPD, i. e., a low-attenuation area on chest HRCT and impaired diffusing capacity of the lung on pulmonary function test-

▶ **Table 1** Characteristics of the study patients at baseline.

Number	16
Female/Male	16/0
Age (years)	81.6 ± 4.1
Height (cm)	151.6 ± 5.4
Weight (kg)	52.1 ± 5.7
BMI (kg/m^2)	22.7 ± 2.5
Smoking history (CS/ES/NS)	0/0/16
Duration of asthma (year)	20.5 ± 16.1
IgE (IU/mL)	184.3 ± 254.3
Number of patients with positive specific IgE	9
ICS (µg/day, equiv. BDP)	778.3 ± 200.3
+ LABA	16
+ LTRA	8
+ Theophylline	6
Total ACT score	19.9 ± 3.1
FVC (L)	1.97 ± 0.54
FVC (%pred)	91.2 ± 22.6
FEV_1 (L)	1.13 ± 0.31
FEV_1 (%pred)	68.9 ± 19.0
FEV_1/FVC (%)	57.7 ± 10.1
MEF_{25-75} (L/sec)	0.42 ± 0.18
MEF_{25-75} (%pred)	21.8 ± 9.6
MEF_{50} (L/sec)	0.62 ± 0.30
MEF_{50} (%pred)	26.5 ± 13.1
MEF_{75} (L/sec)	0.14 ± 0.06
MEF_{75} (%pred)	22.7 ± 13.9
DLco (mL/min/mmHg)	15.64 ± 4.91
DLco (%)	90.8 ± 9.5
DLco/VA (mL/min/mmHg/L)	4.94 ± 1.19
DLco/VA (%)	103.9 ± 16.2
monthly mean morning PEF (L/min)	229.9 ± 70.4
monthly mean evening PEF (L/min)	259.8 ± 53.4
ins R5 (cmH_2O/L/sec)	5.23 ± 3.35
ins R20 (cmH_2O/L/sec)	3.86 ± 2.22
ins R5-R20 (cmH_2O/L/sec)	1.38 ± 1.15
ins X5 (cmH_2O/L/sec)	− 2.02 ± 1.84
ins Fres (Hz)	14.39 ± 5.19
ins ALX (cmH_2O/L/sec x Hz)	13.75 ± 17.46

ACT, Asthma Control Test; ALX, low-frequency reactance area; BDP, beclometasone dipropionate; BMI, body mass index; DLco, diffusing capacity of lung for carbon monoxide; DLco/VA, diffusing capacity of lung for carbon monoxide divided by the alveolar volume; FEV_1, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; Fres, resonant frequency; ICS, inhaled corticosteroid; LABA, long-acting β2-adrenoceptor agonist; LTRA, leukotriene receptor antagonists; MEF_{25-75}, maximal expiratory flow between 25 % and 75 % of FVC; MEF_{50}, maximal expiratory flow at 50 % of FVC; MEF_{75}, maximal expiratory flow at 75 % of FVC; PEF, peak flow; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; X5, respiratory system reactance at 5 Hz

ing [18]. We thought that Tio-Res mainly ameliorated the asthma pathophysiology, rather than COPD pathophysiology, resulting in the clinical efficacy. All of the study patients were female. The reasons for this phenomenon may include the following points: i) Japanese male asthmatic patients have a higher smoking history (79.7 % vs 35.3 % in female) [19], and an active smoking history was one of the exclusion criteria; ii) males sometimes have benign prostatic hyperplasia, which is a contraindication for long-acting muscarinic antagonists (LAMA).



▶ **Fig. 1** Change in ACT score before and after a minimum of one year of Tio-Res 5 µg/day treatment (* $p < 0.05$, significantly different from baseline).

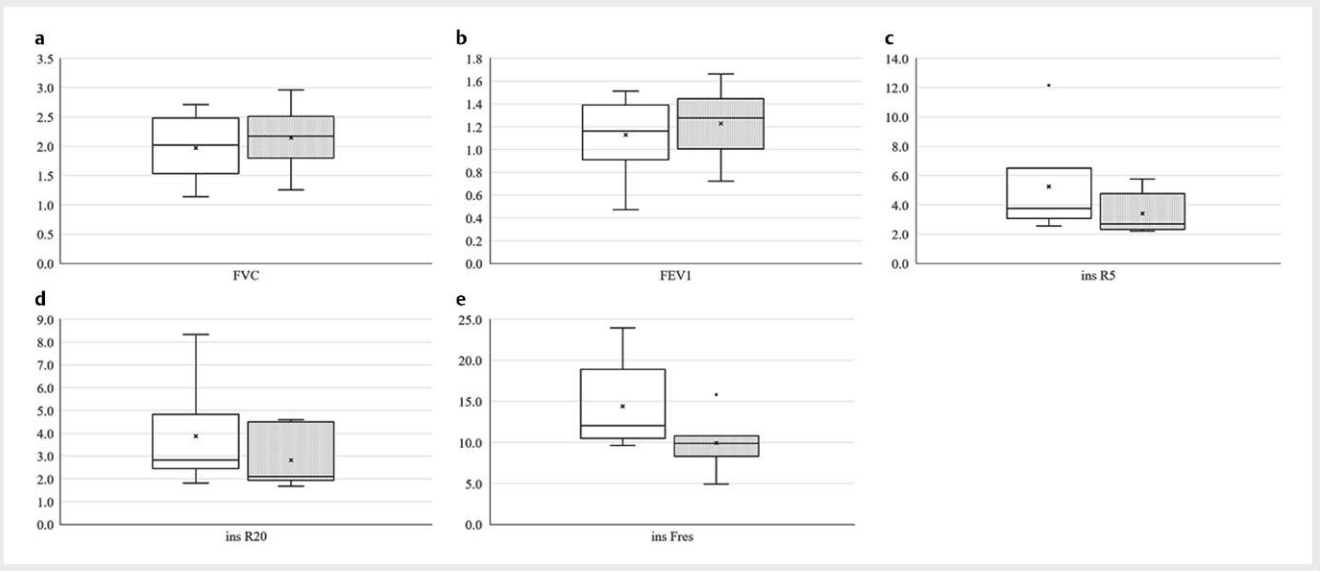
Despite LABA administration, add-on Tio-Res may have additional bronchodilating effects in never-smokers with asthma for the following reasons: i) crosstalk may occur between muscarinic receptors and β2-adrenoceptors [20]; ii) 16 β2-adrenoceptor polymorphisms influence the down-regulating stimulus of bronchodilation caused by the continuous use of β2-adrenoceptor agonists [21, 22] and the bronchodilating effect of tiotropium [23]; iii) some patients with bronchial asthma react to tiotropium but not to salmeterol [24]; iv) there is a regional difference in muscarinic receptors and β2-adrenoceptors, i. e., muscarinic receptors are more highly expressed in the larger airways, whereas β2-adrenoceptors are more highly expressed in the distal airways[25]; v) there are aging effects on respiratory structure and function, i. e., destruction of the peripheral respiratory tract, and a decrease in the number and sensitivity of β2-adrenoceptors despite preservation of muscarinic receptor sensitivity [9, 26]. Several animal studies have reported that tiotropium and other selective muscarinic receptor antagonists suppressed inflammation [27–31] and subsequent airway remodeling [32–37]. It is possible that tiotropium-induced bronchodilation inhibits bronchoconstriction-associated remodeling [11]. Though there is no evidence that tiotropium inhibits or improves remodeling in vivo, it may ameliorate inflammation and airway remodeling in patients with asthma.

Since the 1950's, the FOT has been used as a noninvasive method for measuring respiratory resistance (Rrs) and Xrs during tidal breathing [37, 38]. The multi-frequency oscillation technique was

▶ **Table 2** Changes in ACT total score, pulmonary function, PEF and inspiratory phase Rrs or Xrs (baseline to after the addition of Tio-Res).

	Baseline	After Tio-Res	The rate of change (%)
ACT	19.92 ± 3.12	23.56 ± 1.67	12.16 ± 10.14
FVC (L)	1.97 ± 0.54	2.14 ± 0.48 *	12.15 ± 24.62
FVC (%pred)	91.2 ± 22.6	100.5 ± 18.0 * *	14.08 ± 25.10
FEV_1 (L)	1.13 ± 0.31	1.23 ± 0.28 * *	12.03 ± 15.28
FEV_1 (%pred)	68.9 ± 19.0	75.9 ± 16.5 * *	13.41 ± 14.72
FEV_1/FVC (%)	57.7 ± 10.1	58.5 ± 12.0	0.94 ± 7.35
MEF_{25-75} (L/sec)	0.42 ± 0.18	0.49 ± 0.22 *	16.79 ± 15.75
MEF_{25-75} (%pred)	21.8 ± 9.6	25.2 ± 10.6 *	18.17 ± 16.42
MEF_{50} (L/sec)	0.62 ± 0.30	0.74 ± 0.41	19.62 ± 26.65
MEF_{50} (%pred)	26.5 ± 13.1	31.5 ± 17.0	20.70 ± 26.31
MEF_{75} (L/sec)	0.14 ± 0.06	0.17 ± 0.07	20.42 ± 36.2
MEF_{75} (%pred)	22.7 ± 13.9	25.5 ± 13.0	22.70 ± 36.71
morning PEF (L/min)	229.9 ± 70.4	253.8 ± 70.1 * *	11.99 ± 6.86
evening PEF (L/min)	259.8 ± 53.4	277.4 ± 47.0 *	11.00 ± 8.48
R5 (cmH_2O/L/sec)	5.23 ± 3.35	3.41 ± 1.36 *	-28.22 ± 14.25
R20 (cmH_2O/L/sec)	3.86 ± 2.22	2.82 ± 1.24 *	-22.17 ± 17.11
R5-R20 (cmH_2O/L/sec)	1.38 ± 1.15	0.59 ± 0.29 *	-41.02 ± 36.69
X5 (cmH_2O/L/sec)	-2.02 ± 1.84	-0.82 ± 0.60 *	-44.35 ± 39.13
Fres (Hz)	14.39 ± 5.19	9.92 ± 3.26 *	-27.26 ± 23.69
ALX (cmH_2O/L/sec x Hz)	13.75 ± 17.46	3.95 ± 3.79 *	-51.07 ± 36.97

* * $p < 0.01$, * $p < 0.05$ were significantly different from baseline; ALX, low-frequency reactance area; FEV_1, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; Fres, resonant frequency; MEF_{25-75}, maximal expiratory flow between 25 % and 75 % of FVC; MEF_{50}, maximal expiratory flow at 50 % of FVC; MEF_{75}, maximal expiratory flow at 75 % of FVC; PEF, peak flow; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; Rrs, respiratory resistance; X5, respiratory system reactance at 5 Hz



▶ **Fig. 2** The box-and-whisker plot with FVC (2-1), FEV_1 (2-2), R5 (2-3), R20 (2-4) and Fres (2-5) before and after a minimum of one year of Tio-Res 5 µg/day treatment. Measurements in before (open bar) or after (dotted bar) the addition of Tio-Res.

▶ **Table 3** Correlation between pulmonary function and Rrs or Xrs in inspiratory phase at baseline.

	R5	R20	R5-R20	X5	Fres	ALX
FEV_1	−0.393	−0.321	−0.536	0.794 *	−0.891 * *	−0.842 *
FEV_1 (%predicted)	−0.200	−0.042	−0.676 *	0.685 *	−0.806 *	−0.733 *
FEV1/FVC	−0.464	−0.321	−0.536	0.536	−0.607	−0.643
MEF_{25-75}	−0.214	−0.179	−0.393	0.571	−0.750	−0.679
MEF_{25-75} (%predicted)	−0.214	−0.179	−0.393	0.571	−0.750	−0.679
MEF_{50}	−0.321	−0.250	−0.464	0.607	−0.750	−0.714
MEF_{50} (%predicted)	−0.107	−0.036	−0.286	0.500	−0.643	−0.607
MEF_{75}	−0.205	−0.170	−0.402	0.688	−0.777	−0.741
MEF_{75} (%predicted)	−0.286	−0.250	−0.071	0.714	−0.821 *	−0.786

* * $p < 0.01$, * $p < 0.05$ were significantly correlate between pulmonary function and respiratory impedance.; ALX, low-frequency reactance area; FEV_1, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; Fres, resonant frequency; MEF_{25-75}, maximal expiratory flow between 25 % and 75 % of FVC; MEF_{50}, maximal expiratory flow at 50 % of FVC; MEF_{75}, maximal expiratory flow at 75 % of FVC; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; Rrs, respiratory resistance; X5, respiratory system reactance at 5 Hz; Xrs, respiratory system reactance

developed from FOT, and the difference between the two methods is based on the type of airwave. In this study, we used the MostGraph-01 FOT machine. In a recent MostGraph study, less Xrs variation was observed in the inspiratory phase than in the expiratory phase in patients with COPD or bronchial asthma[39]. Therefore, we investigated changes in inspiratory impedance before and after add-on Tio-Res. This is the first study comparing respiratory impedance before and after tiotropium administration in asthmatics, and we found that Tio-Res improved both the Rrs and Xrs. In our study that targeted never-smoking, elderly asthmatics with irreversible airflow limitation, it was confirmed that the following points were similar to the previous studies: i) regarding the extent of change, Rrs and Xrs improved more dramatically than conventional pulmonary function [40–42]; ii) R5-R20, reflected as uneven ventilation, was decreased by Tio-Res [43, 44]; iii) Xrs was strongly related to FEV_1 similar to previous results in stable asthmatics who have a partial smoking history [39, 45, 46]; iv) Rrs and frequency dependence of Rrs increase more in asthmatics in a severity-dependent fashion [47], and our study patients showed a greater degree of Rrs than that observed in less severe and less obstructed never-smoking asthmatics [48].

Our study has several limitations. First, all of our study patients were female; thus, the study population deviated from the general population. Second, it was a single-center retrospective study and included only 16 patients. Third, our study did not contain a control group, so a placebo effect of Tio-Res cannot be ruled out. Fourth, we did not assess patient-related outcomes, such as quality of life and exacerbations.

Conclusions

Our data suggest that add-on Tio-Res therapy improves symptoms, pulmonary function, and respiratory impedance in never-smoking elderly asthmatics with irreversible airflow limitation despite the use of high-dose ICS plus LABA. Tio-Res may improve clinical indicators in asthmatics over 75 years old with irreversible airflow limitation not related to smoking or COPD, and it may be beneficial in preventing asthma deaths.

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Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

[1] Chung KF, Wenzel SE, Brozek JL et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343–373

[2] Ichinose M, Sugiura H, Nagase H et al. Japanese guidelines for adult asthma 2017. Allergol Int. 2017; 66: 163–189

[3] Ministry of Health, Labour and Welfare. [Japanese Population Survey 2016]

[4] Peters SP, Kunselman SJ, Icitovic N et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 2010; 363: 1715–1726

[5] Paggiaro P, Halpin DM, Buhl R et al. The effect of tiotropium in symptomatic asthma despite low- to medium-dose inhaled corticosteroids: A randomized controlled trial. J Allergy Clin Immunol Pract 2016; 4: 104–113.e102

[6] Kerstjens HA, Engel M, Dahl R et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 2012; 367: 1198–1207

[7] Kerstjens HA, Disse B, Schröder-Babo W et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial. J Allergy Clin Immunol 2011; 128: 308–314

[8] Koga T, Oshita Y, Kamimura T et al. Characterisation of patients with frequent exacerbation of asthma. Respir Med. 2006; 100: 273–278

[9] Braman SS, Kaemmerlen JT, Davis SM. Asthma in the elderly. A comparison between patients with recently acquired and long-standing disease. Am Rev Respir Dis 1991; 143: 336–340

[10] Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging 2006; 1: 253–260

[11] Grainge CL, Lau LC, Ward JA et al. Effect of bronchoconstriction on airway remodeling in asthma. N Engl J Med 2011; 364: 2006–2015

[12] Nathan RA, Sorkness CA, Kosinski M et al. Development of the asthma control test: A survey for assessing asthma control. J Allergy Clin Immunol 2004; 113: 59–65

[13] The Committee of Pulmonary Physiology, J. R. S., Guidelines for Pulmonary Function Tests. Spirometry, Flow Volume Cutve, Diffussin Capacity of the Lung. Japanese Respiratory Society 2004

[14] Kerstjens HA, Moroni-Zentgraf P, Tashkin DP et al. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. Respir Med 2016; 117: 198–206

[15] Huang S, Vasquez MM, Halonen M et al. Asthma, airflow limitation and mortality risk in the general population. Eur Respir J 2015; 45: 338–346

[16] Osborne ML, Pedula KL, O'Hollaren M et al. Assessing future need for acute care in adult asthmatics: The Profile of Asthma Risk Study: A prospective health maintenance organization-based study. Chest 2007; 132: 1151–1161

[17] Loymans RJ, Honkoop PJ, Termeer EH et al. Identifying patients at risk for severe exacerbations of asthma: Development and external validation of a multivariable prediction model. Thorax. 2016; 71: 838–846

[18] Hashimoto S, Ichinose M, Tamaoki J et al. The JRS guidelines for the Management of ACO. Nihon Kokyuki Gakkai Zasshi. Suppl 2017 1–104

[19] Ikeue T, Nakagawa A, Furuta K et al. [The prevalence of cigarette smoking among asthmatic adults and association of smoking with emergency department visits]. Nihon Kokyuki Gakkai Zasshi 2010; 48: 99–103

[20] Roux E, Molimard M, Savineau JP et al. Muscarinic stimulation of airway smooth muscle cells. Gen Pharmacol 1998; 31: 349–356

[21] Israel E, Chinchilli VM, Ford JG et al. Use of regularly scheduled albuterol treatment in asthma: Genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet 2004; 364: 1505–1512

[22] Israel E, Drazen JM, Liggett SB et al. The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. Am J Respir Crit Care Med 2000; 162: 75–80

[23] Park HW, Yang MS, Park CS et al. Additive role of tiotropium in severe asthmatics and Arg16Gly in ADRB2 as a potential marker to predict response. Allergy 2009; 64: 778–783

[24] Peters SP, Bleecker ER, Kunselman SJ et al. Predictors of response to tiotropium versus salmeterol in asthmatic adults. J Allergy Clin Immunol 2013; 132: 1068–1074.e1061

[25] Ikeda T, Anisuzzaman AS, Yoshiki H et al. Regional quantification of muscarinic acetylcholine receptors and β-adrenoceptors in human airways. Br J Pharmacol 2012; 166: 1804–1814

[26] Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. Eur Respir J 1999; 13: 197–205

[27] Buels KS, Jacoby DB, Fryer AD. Non-bronchodilating mechanisms of tiotropium prevent airway hyperreactivity in a guinea-pig model of allergic asthma. Br J Pharmacol 2012; 165: 1501–1514

[28] Bosnjak B, Tilp C, Tomsic C et al. Tiotropium bromide inhibits relapsing allergic asthma in BALB/c mice. Pulm Pharmacol Ther 2014; 27: 44–51

[29] Cao R, Dong XW, Jiang JX et al. M(3) muscarinic receptor antagonist bencycloquidium bromide attenuates allergic airway inflammation, hyperresponsiveness and remodeling in mice. Eur J Pharmacol 2011; 655: 83–90

[30] Ohta S, Oda NI, Yokoe T et al. Effect of tiotropium bromide on airway inflammation and remodelling in a mouse model of asthma. Clin Exp Allergy 2010; 40: 1266–1275

[31] Damera G, Jiang M, Zhao HA et al. Aclidinium bromide abrogates allergen-induced hyperresponsiveness and reduces eosinophilia in murine model of airway inflammation. Eur J Pharmacol 2010; 649: 349–353

[32] Kang JY, Rhee CK, Kim JS et al. Effect of tiotropium bromide on airway remodeling in a chronic asthma model. Ann Allergy Asthma Immunol 2012; 109: 29–35

[33] Gosens R, Bos IS, Zaagsma J et al. Protective effects of tiotropium bromide in the progression of airway smooth muscle remodeling. Am J Respir Crit Care Med 2005; 171: 1096–1102

[34] Bos IS, Gosens R, Zuidhof AB et al. Inhibition of allergen-induced airway remodelling by tiotropium and budesonide: a comparison. Eur Respir J 2007; 30: 653–661

[35] Kistemaker LE, Bos IS, Menzen MH et al. Combination therapy of tiotropium and ciclesonide attenuates airway inflammation and remodeling in a guinea pig model of chronic asthma. Respir Res. 2016; 17: 13

[36] Kistemaker LE, Bos ST, Mudde WM et al. Muscarinic M_3 receptors contribute to allergen-induced airway remodeling in mice. Am J Respir Cell Mol Biol 2014; 50: 690–698

[37] Oostveen E, MacLeod D, Lorino H et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J 2003; 22: 1026–1041

[38] Dubois AB, Brody AW, Lewis DH et al. Oscillation mechanics of lungs and chest in man. J Appl Physiol 1956; 8: 587–594

[39] Mori K, Shirai T, Mikamo M et al. Colored 3-dimensional analyses of respiratory resistance and reactance in COPD and asthma. COPD. 2011; 8: 456–463

[40] Shirai T, Kurosawa H. Clinical Application of the Forced Oscillation Technique. Intern Med. 2016; 55: 559–566

[41] Shimizu Y, Kamiyoshihara M, Okajo J et al. Tracheobronchial stenosis evaluated by inspiratory and expiratory three-dimensional computed tomography and impulse oscillation with three-dimensional color imaging in a patient with relapsing polychondritis. J Biol Regul Homeost Agents 2014; 28: 325–331

[42] Matsuno O, Komori C, Hang Y et al. Effectiveness of omalizumab in a patient with severe asthma, low serum IgE level, and lack of sensitized allergens induced by oral steroid therapy: the usefulness of impulse oscillation for assessment of omalizumab therapy. J Asthma 2012; 49: 839–842

[43] Lándsér FJ, Nagles J, Demedts M et al. A new method to determine frequency characteristics of the respiratory system. J Appl Physiol 1976; 41: 101–106

[44] Williamson PA, Clearie K, Menzies D et al. Assessment of small-airways disease using alveolar nitric oxide and impulse oscillometry in asthma and COPD. Lung. 2011; 189: 121–129

[45] Tsuburai T, Suzuki S, Tsurikisawa N et al. [Use of forced oscillation technique to detect airflow limitations in adult Japanese asthmatics]. Arerugi. 2012; 61: 184–193

[46] Shirai T, Mori K, Mikamo M et al. Respiratory mechanics and peripheral airway inflammation and dysfunction in asthma. Clin Exp Allergy 2013; 43: 521–526

[47] Cavalcanti JV, Lopes AJ, Jansen JM et al. Detection of changes in respiratory mechanics due to increasing degrees of airway obstruction in asthma by the forced oscillation technique. Respir Med 2006; 100: 2207–2219

[48] Kitaguchi Y, Yasuo M, Hanaoka M. Comparison of pulmonary function in patients with COPD, asthma-COPD overlap syndrome, and asthma with airflow limitation. Int J Chron Obstruct Pulmon Dis 2016; 11: 991–997