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
Bronchial asthma, Irreversible airflow limitation, Never smoking, Multi-frequency oscillation technique, Tiotropium Respimat®

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 β₂-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 FEV₁ (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
FEV₁ 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  
MEF25–75  maximal expiratory flow between 25% and 75% of FVC  
MEF50  maximal expiratory flow at 50% of FVC  
MEF75  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 β2-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 (FEV1/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 ASS, SESS peak flow meter (Philips Co., Amsterdam, Netherlands). Predicted values for FVC and FEV1 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, FEV₁, and FEV₁/FVC were 1.971 L (pred, 91.2%), 1.131 L (pred, 68.9%), and 57.7%, respectively. The mean MEF₂₅-₇₅, MEF₅₀, and MEF₂₀ were 0.421/sec (pred, 21.8%), 0.621/sec (pred, 26.5%), and 0.141/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 Table 1, and the FVC (1.97 to 2.14, p < 0.05), FEV₁ (1.13 to 1.23, p < 0.01), MEF₂₅-₇₅ (0.42 to 0.49, p < 0.05), mPEF (229.9 to 253.8, p < 0.01), and ePEF (259.8 to 277.4, 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), 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 inspiratory impedance (Table 2). Several measurements were illustrated as box-and-whisker plot (Table 2). Significant correlation between inspiratory phase R5-R20 or reactance (Xrs) values and FEV₁ or %pred FEV₁ 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 ≥800μg/day) plus LABA. The addition of Tio-Res significantly improved FEV₁ 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 FEV₁/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/m²) | 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 |
| FEV₁ (L) | 1.13±0.31 |
| FEV₁ (%pred) | 68.9±19.0 |
| FEV₁/FVC (%) | 57.7±10.1 |
| MEF₂₅-₇₅ (L/sec) | 0.42±0.18 |
| MEF₂₅-₇₅ (%pred) | 21.8±9.6 |
| MEF₅₀ (L/sec) | 0.62±0.30 |
| MEF₅₀ (%pred) | 26.5±13.1 |
| MEF₁₅ (L/sec) | 0.14±0.06 |
| MEF₁₅ (%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 RS (cmH₂O/L/sec) | 5.23±3.35 |
| ins R₂₀ (cmH₂O/L/sec) | 3.86±2.22 |
| ins R₅-R₂₀ (cmH₂O/L/sec) | 1.38±1.15 |
| ins X₅ (cmH₂O/L/sec) | –2.02±1.84 |
| ins Fres (Hz) | 14.39±5.19 |
| ins ALX (cmH₂O/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; FEV₁, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β₂-adrenoceptor agonist; LTRA, leukotriene receptor antagonists; MEF₂₅-₇₅, maximal expiratory flow between 25% and 75% of FVC; MEF₅₀, maximal expiratory flow at 50% of FVC; MEF₁₅, 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).

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...
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. 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.

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

<table>
<thead>
<tr>
<th></th>
<th>RS</th>
<th>R20</th>
<th>R5-R20</th>
<th>X5</th>
<th>Fres</th>
<th>ALX</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>−0.393</td>
<td>−0.321</td>
<td>−0.536</td>
<td>0.794 *</td>
<td>−0.891 *</td>
<td>−0.842 *</td>
</tr>
<tr>
<td>FEV1 (%predicted)</td>
<td>−0.200</td>
<td>−0.042</td>
<td>−0.676 *</td>
<td>0.685 *</td>
<td>−0.806 *</td>
<td>−0.733 *</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>−0.464</td>
<td>−0.321</td>
<td>−0.536</td>
<td>0.536</td>
<td>−0.607</td>
<td>−0.643</td>
</tr>
<tr>
<td>MEF25,75</td>
<td>−0.214</td>
<td>−0.179</td>
<td>−0.393</td>
<td>0.571</td>
<td>−0.750</td>
<td>−0.679</td>
</tr>
<tr>
<td>MEF25,75 (%predicted)</td>
<td>−0.214</td>
<td>−0.179</td>
<td>−0.393</td>
<td>0.571</td>
<td>−0.750</td>
<td>−0.679</td>
</tr>
<tr>
<td>MEF50</td>
<td>−0.321</td>
<td>−0.250</td>
<td>−0.464</td>
<td>0.607</td>
<td>−0.750</td>
<td>−0.714</td>
</tr>
<tr>
<td>MEF50 (%predicted)</td>
<td>−0.107</td>
<td>−0.036</td>
<td>−0.286</td>
<td>0.500</td>
<td>−0.643</td>
<td>−0.607</td>
</tr>
<tr>
<td>MEF75</td>
<td>−0.205</td>
<td>−0.170</td>
<td>−0.402</td>
<td>0.688</td>
<td>−0.777</td>
<td>−0.741</td>
</tr>
<tr>
<td>MEF75 (%predicted)</td>
<td>−0.286</td>
<td>−0.250</td>
<td>−0.071</td>
<td>0.714</td>
<td>−0.821 *</td>
<td>−0.786 *</td>
</tr>
</tbody>
</table>

* * p < 0.01, * p < 0.05 were significantly correlate between pulmonary function and respiratory impedance.; ALX, low-frequency reactance area; FEV1, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; MEF25,75, maximal expiratory flow between 25 % and 75 % of FVC; MEF50, maximal expiratory flow at 50 % of FVC; MEF75, 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.

Fig. 2 The box-and-whisker plot with FVC (2-1), FEV1 (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.
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.

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