Short-term effects of tiotropium on the pulmonary function and quality of life (QOL) in patients at risk and with mild chronic obstructive pulmonary disease (COPD)

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Abstract
Purpose: Although the short-term effects of tiotropium for patients with Stage II-IV COPD have been established, the effects on patients in earlier stages are not known. We studied the short-term effects of tiotropium on pulmonary function, quality of life (QOL), and clinical symptoms in patients at risk for and with mild COPD.
Subjects and methods: The subjects enrolled the study consist of 85 patients who visited the clinics due to respiratory symptoms, were more than 40 years old, and had a smoking history of more than 10 pack-years were enrolled. They were divided into an At risk-Stage I COPD group and a Stages II-IV COPD group. After the administration of tiotropium for 12 weeks, the changes in the pulmonary function test, QOL, and subjective symptoms were compared before and after the therapy.
Results: Tiotropium increased the FEV1, FVC, and IC and improved the SGRQ scores in the patients in the Stage II-IV COPD group, while it did not cause a significant difference in the At risk-Stage I groups. Some patients in the At risk-Stage I group who experienced an improvement in their subjective symptoms.
Conclusions: We could not show that the patients in the At risk-Stage I group benefited from tiotropium. However, some patients in the At risk-Stage I groups showed improvements in their symptoms. Tiotropium may be effective to relieve symptoms in some patients even when they are in the At risk-Stage I groups.

Key Words: COPD, bronchodilators, tiotropium, quality of life, symptoms

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Tiotropium is one of the most effective long acting bronchodilators\cite{1, 2, 6, 7}. A post hoc analysis of randomized controlled trials has suggested that the initiation of tiotropium at earlier stages improves pulmonary function and HRQOL\cite{8}. The administration of tiotropium from earlier stages may be a promising strategy in the management of COPD.

Tiotropium has been shown to be effective for patients with stages II-IV COPD\cite{1, 2}. On the other hand, the effect on earlier stages of COPD has not been well documented. We hypothesized that the administration of tiotropium to patients at risk and with mild COPD would relieve the clinical symptoms, improves the pulmonary functions, and QOL. To test the hypothesis, we conducted a single-arm, prospective clinical study in which tiotropium was administered for 12 weeks to the COPD patients, and the change in their pulmonary function, the health status as measured by the Saint George's Respiratory Questionnaire (SGRQ)\cite{9, 10}, and the subjective change in their clinical symptoms were compared between the At risk-Stage I COPD group and the Stage II-IV COPD group.

**Methods**

**Subjects**

This study was approved by the ethics committees of the member hospitals of the Saitama Northwest COPD Research Group. Patients who visited member hospitals or clinics of the group between March 2005 and February 2006 complaining of respiratory symptoms, such as chronic cough, sputum and dyspnea on exertion, were invited to enroll if: 1) they were more than 40 years old; and 2) they had smoked more than 10 pack-years. They were excluded if: 1) they had diseases other than COPD that may cause dyspnea; 2) they had a history of asthma; or 3) they had a recent respiratory tract infection. Written informed consent was obtained before any study procedures were undertaken.

**Protocol**

The dose of tiotropium (Spiriva(R); Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT) that was used for daily clinical practice (18 µg once daily)\cite{11} was also used in the current study. On the screening visit, the patients underwent pulmonary function testing to classify themselves into the At risk-Stage I group or the Stages II-IV group based on the GOLD guideline\cite{2}. The patients were evaluated using a pulmonary function test (measured on Weeks 0, 4 and 12), the SGRQ (performed on Weeks 0 and 12) and the inquiry on the change of their clinical symptoms that included cough, sputum and dyspnea (performed on Week 12). The appearance of adverse events was monitored during the entire study period.

**Pulmonary function test**

The pulmonary function test was performed using an office spirometer, where the forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and inspiratory capacity (IC) were measured. For each measurement, the values obtained before and 20 min after an inhalation of a short-acting beta2-agonist (salbutamol 200 µg) were recorded. The values of the pulmonary function tests obtained on Day 0, immediately before and after the administration of the first dose of tiotropium, were defined as the pre- and post-salbutamol baseline values\cite{12}.

**SGRQ**

The SGRQ contains 50 questions covering 3 domains (symptoms, activity, and impact) each of which were scored from 0 (best health) to 100 (worst health). A 4-point change was considered significant\cite{13}, and we scored is as equal to or more than 4-point decreases as an improvement, equal to or more than 4-point increases as a worsening, and the scores in-between as a stable condition.

**Inquiry on the clinical symptoms**

On Week 12, the patients were asked how their cough, sputum and dyspnea changed over the 12-week treatment period, and they chose the answers from among the categories of improvement, stable symptoms and worsening.

**Statistical analysis**

The statistical analyses were performed using the SAS software package (version 9.13). The differences between the pre- and post-treatment values for both the pulmonary function test and the SGRQ were tested by Student’s paired t-test. The data were reported as the means ± standard deviation (SD). P-values less than 0.05 were considered to be statistically significant.

**Results**

**Subjects**

A total of 85 patients were enrolled, of which 78 completed the study. The characteristics of the patients who completed the study did not show any significant differences between the At risk-Stage I and Stages II-IV groups (Table 1). Seven subjects discontinued: 4 were due to adverse events; 3 did not visit the hospitals or clinics for unknown reasons.

**Pulmonary function test**

Our study was performed in the daily clinical setting, where pulmonary function testing that required expensive equipment was not practical. We therefore investi-
The patients in the Stage II-IV group presented more symptoms than those in the earlier stages of COPD. The result is shown in Figure 3. Although the proportion was smaller in the Stage II-IV group, some patients in the At risk-Stage I group felt that their symptoms were relieved, especially cough and dyspnea. The result shows that there are patients, even in the At risk-Stage I group, who benefit from tiotropium based on improvements in their clinical symptoms.

Adverse events
The overall incidence of adverse events was 14.0% (1 patient (1.2%) in the At risk-stage I group; 11 patients (12.8%) in the Stage II-IV group). Three patients (3.5%) in Stages II-IV discontinued the trial due to probable drug-related adverse events that included ileus, drug allergy, and the aggravation of prostate hypertrophy. One patient (1.2%) experienced an acute exacerbation of COPD and dropped out from the study. The most common adverse event was dry mouth (2 patients (2.3%) in the At risk-stage I group; 3 patients (3.5%) in the Stage II-IV group), although it was mild and none of the patients stopped taking tiotropium. Other adverse events observed were frequent urination (3 patients (3.5%)), upper respiratory tract infection (1 patient (1.2%)), and dizziness (1 patient (1.2%)).

Discussion
It has been shown that tiotropium is effective for patients with moderate to severe COPD. In the current study, we investigated whether patients in the earlier stages of COPD benefit from tiotropium.

We found that the patients in the Stage II-IV group showed a significant improvement in the pulmonary function test, and this is consistent with the results of the previous reports. We could not find any improvement in the pulmonary function test in the patients in the At risk-stage I group: even in a model calculation, where the number of the patients was assumed to have doubled, we could not obtain a significant difference. Tiotropium may therefore provide little benefit in the pulmonary function for patients in the At risk-Stage I group.

We also had a negative result for the improvement of the SGRQ score in the patients in the At risk-Stage I group. Our study was performed in an outpatient clinic setting, where we found that most of the patients with At risk-Stage I COPD visit the doctors’ office complaining of cough, sputum, or dyspnea. Their social activity is usually well maintained, because their disease is not severe enough to impair it. We thus focused on cough, sputum, and dyspnea, and investigated the change in them after the tiotropium treatment. Some patients showed an improvement. Since the reason of the visit to the office was for such symptoms, we found that many of the patients were satisfied with the treatment. The patients in the At risk-Stage I groups are not at the risk of dying because of COPD. The important thing for these patients is to fully understand the risk of COPD and relieve their symptoms.

Table 1. Patient characteristics

| At risk-Stage I | Stages II-IV | Overall |
|----------------|-------------|---------|
| No. of subjects | 38          | 40      | 78      |
| Male/female    | 38/0        | 36/0    | 74/4    |
| Age (years)*   | 68.4±7.9    | 69.1±8.0| 68.7±7.9|
| Smoking (pack years)* | 53.2±30.8 | 52.7±25.1| 52.9±26.3|
| Cough          | 28          | 27      | 51      |
| Sputum         | 30          | 26      | 56      |
| Dyspnea        | 30          | 35      | 65      |

*Data are presented as the mean ±SD.
Fig. 1. Pulmonary function test. (A) Values for FEV1, (B) FVC and (C) for IC before and after the tiotropium treatment for the patients who belong to the At risk-Stage I (n=38) and the Stages II-IV (n=40) COPD groups. Error bars indicate standard error. n.s: not significant.
Fig. 2. SGRQ result. (A) A box and whisker plot. A small circle represents the mean, a bar represents the median, a box represents the range for 25-75% values, and error bars represent the range for 10-90% values. (B) The proportions of the patients who presented the improvement, worsening and stable disease for the total as well as each domain of the SGRQ are shown.
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Fig. 3. Change in the clinical symptoms. The proportions of the patients who had an improvement, a worsening and stable symptoms for each group are shown.

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