Acta Med. Okayama, 2017
Vol. 71, No. 5, pp. 453-457

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Clinical Study Protocol

Protective Effects of Bisoprolol against Acute Exacerbation in Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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Although recent retrospective studies suggested that the use of β-blockers appears to help improve the mortality rate and decrease the rate of exacerbation in chronic obstructive pulmonary disease (COPD) patients with heart failure, the effects of β-blockers on COPD patients without heart failure have not been established. Based on previous reports, we have launched a multicenter, prospective, single-arm phase II study to evaluate the preventive effect of the cardioselective β-blocker bisoprolol in COPD exacerbation, in Japanese individuals with moderate-to-severe COPD who do not have heart failure but do have hypertension requiring the use of medication. The primary endpoint is the rate of mild-to-severe COPD exacerbation. The results of this study will clarify whether bisoprolol can prevent exacerbation in COPD patients without heart failure.

Key words: chronic obstructive pulmonary disease, β-blocker, bisoprolol, exacerbation, heart failure

Globally, chronic obstructive pulmonary disease (COPD) is a leading cause of disability, death, and the use of healthcare resources [1]. In Japan, COPD was the tenth leading cause of death in 2015, and the number of COPD patients is projected to increase. COPD is a multisystem disease associated with a number of significant comorbid illnesses (including cardiovascular disease) that can cause or contribute to moderate COPD exacerbations [2].

There are proven benefits to using β-blockers in the treatment of hypertension, ischemic heart disease, and heart failure. However, β-blockers have historically been avoided in asthma treatment because of the risk of acute bronchospasm [3-5]. These concerns also apply to COPD, with evidence of a reduction in forced expiratory volume in one second (FEV_1), increased airway hyper-responsiveness, and inhibition of the bronchodilator response to β-agonists in patients receiving non-selective β-blockers or high doses of cardioselective β-blockers [6,7]. Many physicians are thus reluctant to prescribe β-blockers for patients with concurrent COPD [8].

Several studies have suggested that β-blockers can be

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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

safely used for COPD patients with heart failure [9-13]. In particular, cardioselective β-blockers such as atenolol and bisoprolol are thought to be safe in COPD with heart failure [9,12]. Several research groups proposed that the use of β-blockers might help reduce the mortality rate and improve the rate of exacerbation in COPD patients with heart failure [10-13]. However, most of the preceding reports were of retrospective studies, and thus prospective interventional studies are required for a more definitive assessment of whether β-blockers are associated with the lung function and prognosis in COPD.

Moreover, β-blockers might improve mortality and the rate of exacerbation for COPD patients with heart failure, but their benefit for COPD patients without heart failure has not been well studied. In addition, the populations of the preceding reports were comprised of Europeans and North Americans, and few studies have investigated Japanese subjects.

Therefore, using a prospective interventional study, we wished to examine the use of β-blockers in the management of COPD by assessing whether the β-blockers improve the prognosis. With the above-mentioned background, we have launched an open-labeled, multicenter phase II study aimed at evaluating the preventive effect of bisoprolol in COPD exacerbation. In this study, bisoprolol is used as a cardioselective β-blocker because several reports have shown that bisoprolol can be safely administered to COPD patients with heart failure, compared to other β-blockers. Since some recent studies have already shown the adequacy of using β-blockers in COPD patients with heart failure, this study evaluated COPD patients who do not have heart failure but do have hypertension requiring the use of some medications.

Study Design

This study is a prospective, single-arm, open-labeled phase II trial investigating Japanese patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2-4 COPD, aimed at determining whether bisoprolol has a preventive effect on COPD exacerbation. This is a multicenter trial at 33 institutions affiliated with the Okayama Respiratory Disease Study Group. Fig. 1 provides an overview of the study design.

Ethical Consideration

This study is being conducted in accord with the Declaration of Helsinki, and the protocol has been approved by the institutional review board of each participating hospital (Okayama University Hospital, No. 1612-007). The protocol was registered at the website of the University Hospital Medical Information Network, Japan (protocol identification no. UMIN000024712).

Study Endpoints

The primary endpoint is the rate of moderate-to-severe COPD exacerbation during an observation period of 2 years. Exacerbation is defined as an increase in, or a new onset of, more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting 3 days or more and requiring treatment with an antibiotic or a systemic corticosteroid. Severe exacerbation is defined as an exacerbation that requires hospitalization [14], and mild exacerbation is defined as exacerbation without the need for hospitalization.

Secondary endpoints include the annual decline rate

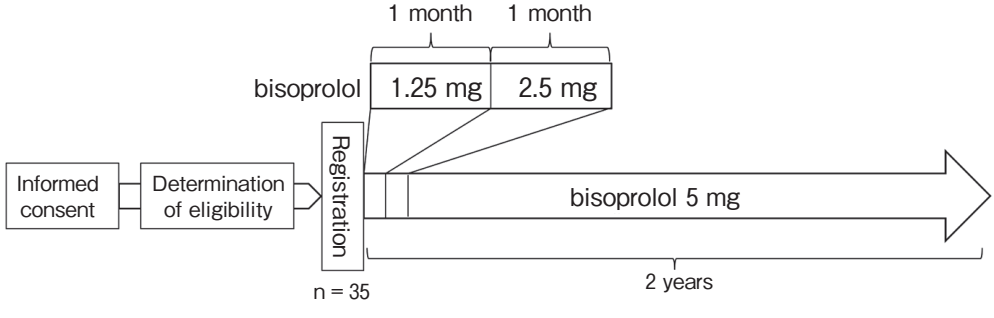

Fig. 1 Overview of the study design.

of post-bronchodilator forced expiratory volume in 1 second (FEV_1), the COPD Assessment Test (CAT) result, the modified Medical Research Council (mMRC) Dyspnea Scale score, the patient's health-related quality of life as measured by the total score on the St. George's Respiratory Questionnaire in its COPD-specific version (SGRQ-C) [15], the brain natriuretic peptide level, the blood pressure control status, and the occurrence of adverse events.

Eligibility Criteria

GOLD stage 2–4 COPD patients with hypertension without heart failure will be recruited to this study. The detailed inclusion and exclusion criteria are listed in Table 1. Written informed consent must be obtained from all patients before registration.

Treatment Methods

After written informed consent has been obtained, eligible patients will receive 1.25 mg bisoprolol once daily. This dosage will then be increased from 1.25 mg/day to 2.5 mg/day at monthly intervals, and up to 5 mg/day if tolerated. The medication will be continued after the end of this study unless the patient wishes todiscontinue the medication or the study reveals disadvantages to using the medication. Treatment will be paused when (1) the patient has a systolic blood pressure value < 100 mmHg, or (2) bradycardia with some symptoms, or (3) a heart rate < 50 bpm. In the case of (1), when the patient's blood pressure recovers to ≥ 110 mmHg, and in the cases of (2) and (3), when their symptoms are remitted and the heart rate has recovered to ≥ 60 bpm, treatment will restart with a dose one step lower than that previously given. All respiratory medi-

Table 1 Patient eligibility

Inclusion criteria
- (1) a diagnosis of chronic obstructive pulmonary disease
- (2) a postbronchodilator FEV_1 (forced expiratory volume in 1 sec) value of ≤70% of the FVC (forced vital capacity)
- (3) a postbronchodilator FEV_1 value ≤80% of the predicted value
- (4) age ≥40 years
- (5) 10 pack-years smoking history
- (6) hypertension
- (7) adequate organ function

Exclusion criteria
- (1) patients with severe (NYHA grade 3 or 4) cardiac failure
- (2) left ventricular contractility ≤40%
- (3) 2nd/3rd-degree atrioventricular block, sinoatrial block, or sick sinus syndrome
- (4) variant angina pectoris
- (5) severe peripheral circulatory disturbance
- (6) pulmonary hypertension from right cardiac failure
- (7) a history of pulmonary resection
- (8) malignancy with a disease-free interval <3 years
- (9) systolic blood pressure of less than 100 mmHg
- (10) cardiac rate <60 bpm on a constant basis
- (11) uncontrolled diabetic mellitus
- (12) hyrotoxicosis
- (13) pheochromocytoma
- (14) psoriasis
- (15) use of supplemental oxygen or with an SpO_2 <90% (or PaO_2 of <60 Torr)
- (16) asthma
- (17) active interstitial pneumonia
- (18) COPD exacerbation or respiratory infection within 4 weeks before registration
- (19) pregnant women
- (20) current use of a β-blocker
- (21) history of hypersensitivity to bisoprolol
- (22) patients considered to be inappropriate for this study by the attending physician

cations and antihypertensive medications except β-blockers will be permitted during the trial.

All of the enrolled patients will be followed for 2 years, and occurrences of moderate-to-severe COPD exacerbation will be recorded. The safety and tolerability assessments include the determination of clinical history, blood pressure, pulse rate, oxygen saturation (SpO_2), 12-lead electrocardiogram, chest X-ray, clinical laboratory tests, pulmonary function test, and adverse event recording.

Statistical Analysis

According to the UPLIFT study, the estimated rate of 2-year moderate exacerbations of GOLD stage 2–4 COPD (tiotropium group) is 67.1% [16]. The authors of a retrospective cohort study in which the effects of β-blockers on COPD patients were investigated reported that the incidence risk ratio representing the impact of β-blockers on the exacerbation rate for total exacerbations was 0.75 over an average 2-year observation period [10]. Expecting an approximate 25% reduction in the exacerbation rate through the use of β-blockers, an estimated incidence of the annual exacerbation rate of 45% and an upper limited incidence of 67% would be assumed with an alpha error of 0.05 and beta error of 0.2; thus, 30 evaluable patients are required [17]. With this in mind, a total of 35 patients are to be recruited to this study, taking into account a percentage of unevaluable patients including those dropping out of approx. 10%. In the present study, no predefined interim analysis will be applied. About 20 eligible patients per year are anticipated; therefore, the recruiting period was set from December 20, 2016 to December 20, 2018. Including the 2-year follow-up period, this study will be performed until December 20, 2021.

The effect of bisoprolol will be evaluated using the exacerbation rate and its 95% confidence interval. The result of an upper confidence limit of $< 67\%$ will reject the null hypothesis.

Discussion

Many physicians are reluctant to use β-blockers for their patients with COPD, although it has been reported that β-blocker use might benefit COPD patients. For example, a large observational study conducted in 1998 of COPD patients after myocardial infarction demonstrated that the β-blockers improved the survival of these COPD patients similarly to otherwise healthy patients, those with heart failure, and older patients [18]. In addition, some studies have suggested that cardioselective β-blockers including bisoprolol are safe for use in COPD patients with heart failure, indicating that the use of β-blockers reduced the mortality rate and decreased the rate of exacerbation [10-13]. However, most of these reports were of retrospective studies of COPD patients with heart failure. The present prospective study, which targets COPD patients without heart failure, thus has great value.

In the reports demonstrating the protective effects of β-blockers against COPD mortality and exacerbation, several potential underlying mechanisms were considered. In one of these reports, it was proposed that the effect of β-blockers might decrease exacerbations arising from cardiovascular causes [19]. Another group speculated that the overexpression of β-receptors by the administration of β-blockers can, in turn, decrease bronchoconstriction [20]. Interestingly, it has also been reported that β-blockers suppress airway inflammation and mucus production [21] and reduce resting tachycardia, an independent predictor of mortality in COPD [22].

In light of these considerations, the cardioselective β-blocker bisoprolol is expected to have a protective effect against exacerbation in COPD and to be able to improve the prognosis of COPD patients. We hope that our multicenter, prospective, single-arm phase II study of the effects of bisoprolol will answer whether this β-blocker could become a new therapeutic strategy for COPD.

Acknowledgments. We thank all investigators in the participating institutions. All authors contributed to the coordination of the study in each hospital. The study received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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