Chronic obstructive pulmonary disease treated with inhaled medium- or high-dose corticosteroids: a prospective and randomized study focusing on clinical efficacy and the risk of pneumonia

Shih-Lung Cheng1,2
Kang-Cheng Su3
Hao-Chien Wang4,∗
Diahn-Wan Gong 3,∗
Pan-Chyr Yang∗

1Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, 2Department of Chemical Engineering and Materials Science, Yuan Ze University, Zhongli City, Taoyuan County, 3Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, 4Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

∗These authors contributed equally to this work

Purpose: Complications of pneumonia development in patients with chronic obstructive pulmonary disease (COPD) receiving inhaled corticosteroid (ICS) therapy have been documented. The aim of this study was to focus on clinical efficacy and the incidence of pneumonia between COPD patients receiving medium and high doses of ICS.

Patients and methods: This prospective, randomized study included COPD patients identified from three tertiary medical centers from 2010 to 2012. The patients were randomized into two groups: high dose (HD; fluticasone 1,000 μg + salmeterol 100 μg/day) and medium dose (MD; fluticasone 500 μg + salmeterol 100 μg/day). Lung function with forced expiratory volume in 1 second (FEV1), forced vital capacity, and COPD-assessment test (CAT) were checked every 2 months. The frequency of acute exacerbations and number of pneumonia events were measured. The duration of the study period was 1 year.

Results: In total, 237 COPD patients were randomized into the two treatment arms (115 in the HD group, 122 in the MD group). The FEV1 level was significantly improved in the patients in the HD group compared with those in the MD group (HD 103.9±26.6 mL versus MD 51.4±19.7 mL, P<0.01) at the end of the study. CAT scores were markedly improved in patients using an HD compared to those using an MD (HD 13±5 versus MD 16±7, P=0.05). There was a significant difference in the percentage of annual rates in acute exacerbations (HD 0.16 versus MD 0.34, P<0.01) between the two groups. The incidence of pneumonia was similar in the two groups (HD 0.08 versus MD 0.10, P=0.38).

Conclusion: COPD patients treated with high doses of ICS had more treatment benefits and no significant increases in the incidence in pneumonia. Higher-dose ICS treatment may be suitable for COPD therapy.

Keywords: chronic obstructive pulmonary disease, pneumonia, inhaled corticosteroids

Introduction

Chronic obstructive pulmonary disease (COPD) is estimated to become the fourth-leading cause of death worldwide despite advanced intensive care.1 COPD is characterized by airflow limitation with a deterioration in lung function, which is usually progressive, with symptoms of dyspnea, productive cough, and sputum. The mechanism of COPD is due to abnormal inflammatory responses of the pulmonary small airways and parenchyma, and is caused by cigarette smoking or other air pollution.2,3 Pulmonary parenchymal inflammation is usually initiated by neutrophils and a number of CD8+ T lymphocytes and macrophages,4,5 and results in overwhelming...
reactive oxygen species production (oxidative stress) and a protease/antiprotease imbalance, both of which have been associated with an increased risk of exacerbation and disease progression. Moreover, COPD has been associated with extrapulmonary manifestations and an increased incidence of pulmonary infection, and patients with COPD complicated with pneumonia who are admitted to hospital have been shown to have more adverse outcomes.

Previous studies have confirmed that receiving inhaled corticosteroid (ICS) regimens can decrease the frequency of COPD exacerbations and improve quality of life. The Global initiative for chronic Obstructive Pulmonary Disease (GOLD) guidelines strongly recommend that group C or D patients should receive ICS treatment combined with a long-acting β-agonist (LABA). Although ICS treatment reduces the exacerbation rate and frequency of COPD, ICS therapy has been reported to increase the risk of developing pneumonia. However, other studies have reported that the risk of pneumonia is not related to ICS usage. Moreover, a large observational study reported that the prior use of ICS was independently associated with a decreased risk of short-term mortality and mechanical ventilation use after hospitalization for pneumonia in patients with COPD. Cheng et al also reported no increased risk between the incidence of pneumonia and dosage of ICS. The optimal dosage of ICS treatment for COPD patients remains unknown.

The advantages and disadvantages between high and medium doses of ICS in combination with a LABA need to be clarified, and the optimal dose of ICS therapy to provide the greatest benefits in terms of anti-inflammation response and lung-function maintenance needs to be elucidated. Only a few prospective studies have focused on these important issues. The aim of the current prospective, randomized study was to investigate treatment efficacy with high and medium doses of fluticasone in combination with salmeterol in COPD patients, with a special focus on lung function and the risk of pneumonia.

Patients and methods

Patients

A prospective, randomized, nonblinded study was performed over 1 year in three tertiary medical centers. COPD was diagnosed according to the medical history, physical examination, chest radiographic findings, and pulmonary function tests suggested by the American Thoracic Society guidelines. The inclusion criteria were chronic airway symptoms and signs with cough and sputum, shortness of breath, wheezing and persistent airway limitations (defined as postbronchodilator forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] <70% and FEV₁ <80% of the predicted value via spirometric data), FEV₁ reversibility after inhalation of 200 µg salbutamol of less than 12% of prebronchodilator FEV₁, and a smoking history of more than 10 pack-years. Subjects (over 40 years old) with COPD diagnosed for over 6 months prior to screening were included in the study.

The exclusion criteria were: life-threatening COPD with acute exacerbations developing within 1 year; patients who had visited the emergency department or had been hospitalized for a COPD attack in the month prior to screening; systemic corticosteroid prescriptions in the 4 weeks before screening; those without a history of smoking or the equivalent of less than 10 pack-years; significant airway reversible responsibility with an asthma pattern; active pulmonary tuberculosis disease; and clinical respiratory tract infections documented in the 4 weeks before screening. Patients receiving medications that would interfere with bronchospasm and/or changes in lung function were also excluded.

Interventions and randomization

The patients were randomized 1:1 into one of two treatment groups: high dose (HD) and medium dose (MD) ICS. The definition of an HD of ICS was fluticasone 1,000 µg/day, and the definition of an MD was fluticasone 500 µg/day. Both treatment groups received salmeterol 100 µg/day, administered via a hydrofluoroalkane pressurized metered-dose inhaler with a space device (GlaxoSmithKline, London, UK). Randomization was conducted centrally by means of a computer-generated random-number sequence.

Definition of an acute exacerbation of COPD was an acute event characterized by a worsening of the patient’s respiratory symptoms beyond normal day-to-day variation leading to a change in medications. Chest radiographs were performed and evaluated by the investigators (respiratory physicians) when an exacerbation of COPD was detected. Pneumonia was diagnosed if there was radiographic evidence of a pulmonary infection (new consolidation and/or infiltrates on the chest radiograph). Sputum Gram staining and bacteria cultures were also checked if tuberculosis infection was suspected clinically. If chest X-rays were not available, the patients were not enrolled into this study.

Assessment of efficacy and safety

During the 52-week study period, the patients underwent evaluations of clinical parameters including spirometry (FEV₁ and FVC) and symptom score with the COPD-assessment...
test (CAT)\(^6\) for interventions. The CAT is a questionnaire assessing globally the impact of COPD on health status. Spirometry, CAT, and clinical parameters were evaluated at study entry, at the 1-month visit, and then at visits every 2 months throughout the study period. The primary end points were comparisons of lung function from entry to the end of the study, and the incidence of pneumonia. The secondary end points included the association of health-related quality of life with CAT scores, and time to first acute exacerbation. Adverse events were documented with spontaneous reporting and patient interviews. Ethical approval was received from the hospital, and informed consent was obtained from all study subjects.

**Statistical analysis**
The sample size calculation for the trial (n=210) provided 90% power to detect a 30% increase in the improvement of lung-function status in the HD group compared with the MD group. Categorical variables were compared by the \(\chi^2\) test, and continuous variables were compared using Student’s \(t\)-test. A \(P\)-value of less than 0.05 was taken to be statistically significant. Fisher’s exact test (qualitative data) or an analysis of variance (quantitative data) was used to assess the homogeneity of the treatment groups. A Hosmer–Lemeshow goodness-of-fit test was performed to help decide whether the model fit the data well. Intention-to-treat analysis was performed for the subjects who were lost to follow-up. All statistical parameters were analyzed using SPSS software version 10.0 (SPSS, Chicago IL, USA).

**Results**

**Recruitment and patient disposition**
This study was initiated in June 2010. A total of 237 patients were randomized into the two treatment arms (115 patients in the HD group, and 122 in the MD group), of whom 217 (91.6%) completed the study and 20 (8.4%) did not (Figure 1). There were 36 patients with bronchial reversibility during the screen period. The rate was 11.8%. These patients were excluded due to the inclusion criteria in the study (FEV\(_1\), reversibility <12%). Among the 20 patients who did not complete the study, 12 withdrew due to a lack of therapeutic benefits (six in each group), four were lost to follow-up, and four withdrew informed consent. They were not out of the study because of adverse events. Exclusion of these data did not affect the efficacy analysis.

**Baseline demographics and characteristics**
Patient demographics and characteristics of the HD and MD groups are listed in Table 1. Most patients (85%) were male, and had an average lung function (FEV\(_1\)) that was classified as GOLD III status (46.1% of predicted in the HD group, and 47.2% of predicted in the MD group). There were no significant differences between the two treatment groups before the run-in study. There were no significant differences in ICS and

**Table 1** Baseline demographic characteristics of study subjects with chronic obstructive pulmonary disease (COPD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD-HD (n=106)</th>
<th>COPD-MD (n=111)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.4±20.3</td>
<td>68±23.4</td>
<td>0.49</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>92/14</td>
<td>93/18</td>
<td>0.64</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>27.4±16.5</td>
<td>29.1±19.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Severity class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD I (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.41</td>
</tr>
<tr>
<td>GOLD II (%)</td>
<td>29 (27.4)</td>
<td>24 (21.6)</td>
<td></td>
</tr>
<tr>
<td>GOLD III (%)</td>
<td>47 (44.3)</td>
<td>51 (45.9)</td>
<td></td>
</tr>
<tr>
<td>GOLD IV (%)</td>
<td>30 (28.3)</td>
<td>36 (32.5)</td>
<td></td>
</tr>
<tr>
<td>FEV(_1), L (% of predicted)</td>
<td>1.24 (46.1)</td>
<td>1.27 (47.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>FVC, L (% of predicted)</td>
<td>2.31 (56.3)</td>
<td>2.26 (54.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>FEV(_1)/FVC (% of predicted)</td>
<td>46.5±18.9</td>
<td>49.7±20.3</td>
<td>0.14</td>
</tr>
<tr>
<td>FEV(_1), reversibility (%)</td>
<td>5.6±3.6</td>
<td>4.9±4.1</td>
<td>0.44</td>
</tr>
<tr>
<td>CAT baseline</td>
<td>18±6</td>
<td>19±7</td>
<td>0.23</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>51 (48.1)</td>
<td>57 (51.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>36 (33.9)</td>
<td>38 (34.2)</td>
<td>0.51</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>11 (11.3)</td>
<td>14 (12.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>18 (16.9)</td>
<td>25 (22.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Medications at baseline R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline (%)</td>
<td>67 (63.2)</td>
<td>69 (62.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Indacaterol (%)</td>
<td>34 (32.1)</td>
<td>37 (33.3)</td>
<td>0.59</td>
</tr>
<tr>
<td>Tiotropium (%)</td>
<td>59 (55.7)</td>
<td>64 (57.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>ICS (%)</td>
<td>41 (38.7)</td>
<td>47 (42.3)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Notes: All values are shown as means ± standard deviation.

Abbreviations: HD, high dose; MD, medium dose; GOLD, Global initiative for chronic Obstructive Lung Disease; FEV\(_1\), forced expiratory volume in 1 second; FVC, forced vital capacity; CAT, COPD-assessment test; CAD, coronary artery disease; CHF, chronic heart failure; R, randomization; ICS, inhaled corticosteroid.
other prescribed medications, including bronchodilator agents and theophylline utilizations, or underlying comorbidities between the two groups either. Mean baseline CAT scores were 18±6 in the HD group and 19±7 in the MD group.

Outcome assessment and measurements

Analysis of the primary end point of pulmonary function status with FEV₁ and FVC revealed that the patients showed improvements in lung function in both treatment groups during the study. However, a greater increase in FEV₁ level was detected in the HD group compared to the MD group (HD 103.9±26.6 mL versus MD 51.4±19.7 mL, P<0.01), and improvements in FVC from baseline in the HD group were observed at every time point measured throughout the study, especially in months 10 and 12 (Figure 2). The level of FVC was also more improved in the HD group than in the MD patients (HD 218.4±46.2 mL versus MD 107.8±38.9 mL, P<0.01) (Figure 3). Patients receiving higher doses of fluticasone had a greater improvement in lung function. Among these patients, levels of lung function were more significantly increased in the GOLD II subjects after higher-dose treatments.

Patient-assessed COPD symptom scores with the CAT were lower in the HD group (15±7) compared to the MD group (16±9) at 6 months. Overall, CAT scores decreased in both groups throughout the study, with a statistically significant difference in favor of the patients in the HD group (13±5 versus 16±7, P=0.05). There was a trend of a higher quality of life among patients who received continuous higher ICS treatment. Absolute changes from baseline regarding decreases in the mean scores of the CAT also showed a significant difference between HD and MD patients (6±2 versus 3±2, P=0.05) at the end of the study.

Seventeen episodes of acute exacerbations were detected in the HD group (0.16 per person-year): seven subjects who visited the emergency department, eight who received additional medication treatment, and two who required hospitalization. However, 38 episodes of acute exacerbations (0.34 per person-year) were noted in the MD group: 18 who visited the emergency department, 21 who required additional medications, and one who required hospitalization. There was a significant difference in the percentage of annual rate in acute exacerbations (0.16 versus 0.34, P<0.01) between the two groups (Table 2). None of the patient’s conditions were ever life-threatening. In addition, there was no obvious difference with regard to the incidence of pneumonia between the two groups (HD 0.08 versus MD 0.10 per person-year, P=0.38). Other side effects, such as hoarseness, were also similar between the two groups (HD 5.7% versus MD 9.0%, P=0.41). Sputum-culture results were also surveyed, and the incidence of Streptococcal pneumonia infection was most common in the COPD patients with pneumonia. Significantly more patients in the MD group

Table 2 Treatment response in chronic obstructive pulmonary disease (COPD) patients with high and medium doses of fluticasone/salmeterol

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD-HD (n=106)</th>
<th>COPD-MD (n=111)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung function after treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁L (% of predicted)</td>
<td>1.35 (56.2)</td>
<td>1.31 (51.7)</td>
<td>0.02*</td>
</tr>
<tr>
<td>FVC, L (% of predicted)</td>
<td>2.53 (54.8)</td>
<td>2.37 (52.5)</td>
<td>0.04*</td>
</tr>
<tr>
<td>FEV₁ change from baseline, mL</td>
<td>103.9±26.6</td>
<td>51.4±19.7</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FEV₁ change in GOLD II</td>
<td>114.0±32.5</td>
<td>73.1±25.6</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FEV₁ change in GOLD III</td>
<td>81.6±28.7</td>
<td>36.4±13.1</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FEV₁ change in GOLD IV</td>
<td>53.2±16.3</td>
<td>18.7±8.4</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FVC change from baseline (mL)</td>
<td>218.4±46.2</td>
<td>107.8±38.9</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FVC change in GOLD II</td>
<td>237.7±41.6</td>
<td>125.6±40.2</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FVC change in GOLD III</td>
<td>168.7±39.3</td>
<td>87.9±38.6</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FVC change in GOLD IV</td>
<td>125.9±35.7</td>
<td>60.2±31.4</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Exacerbation rate (per patient per year)</td>
<td>0.16</td>
<td>0.34</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Hoarseness (per patient per year)</td>
<td>6 (5.7)</td>
<td>10 (9.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Admission rate (per patient per year)</td>
<td>0.02</td>
<td>0.01</td>
<td>0.51</td>
</tr>
<tr>
<td>Pneumonia rate (per patient per year)</td>
<td>0.08</td>
<td>0.10</td>
<td>0.38</td>
</tr>
<tr>
<td>Streptococcal pneumonia, %</td>
<td>5 (29.4)</td>
<td>8 (21.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemophilus parainfluenzae, %</td>
<td>2 (11.8)</td>
<td>9 (23.7)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Klebsiella pneumonia, %</td>
<td>3 (17.6)</td>
<td>5 (13.2)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Notes: *P<0.05; all values are shown as means ± standard deviation.

Abbreviations: HD, high dose; MD, medium dose; GOLD, Global initiative for chronic Obstructive Lung Disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; CAT, COPD-assessment test.

Figure 2 Change in forced expiratory volume in 1 second (FEV₁) in chronic obstructive pulmonary disease patients with high-dose (HD) or medium-dose (MD) treatment. Note: *P<0.05.
Figure 3 Change in forced vital capacity (FVC) in chronic obstructive pulmonary disease patients with high-dose (HD) or medium-dose (MD) treatment.

Note: *P* = 0.05.

had *Haemophilus parainfluenzae* infections than those in the HD group (23.7% versus 11.8%, *P* = 0.02). There were no mycobacterium specimens isolated in this study. No cases of tuberculosis were diagnosed, and no empirical antituberculosis medications were prescribed during the study period.

**Discussion**

This was the first prospective, randomized study to evaluate the efficacy and safety of different ICS doses in the treatment of COPD. Our data showed that therapy with higher ICS doses (fluticasone 1,000 µg/day) in patients with COPD improved lung-function status, decreased the frequency of acute exacerbations, and provided better improvements in symptoms and quality of life compared to those with medium doses of ICS treatment. Most importantly, the risk of developing pneumonia or other side effects did not differ between the two treatment groups. Our findings showed the better treatment efficacy of higher doses of ICS in patients with COPD.

The pathogenesis of COPD is based on airway inflammation caused by cigarette smoke and/or in/outdoor fume exposure. Airway inflammation is characterized by increased numbers of neutrophils, macrophages, and CD8+ lymphocytes. Infiltration of inflammatory cells into the airways occurs in both early and late COPD. As the disease progresses, the small airways fill with inflammatory mucus exudates.27 The presence of inflammation in the airways provides a rationale for using ICS and LABA to treat the disease. Previous studies have documented that ICS treatment decreases the expressions of neutrophils and interleukin 8 in bronchoalveolar lavage fluid in COPD patients28 by suppressing the expressions of Toll-like receptor 4 and lipopolysaccharide-induced interleukin 8 in a dose-dependent fashion.29 Furthermore, ICS treatment has been shown to ameliorate airway-remodeling status by suppressing vascular endothelial growth factor and transforming growth factor-β expressions.30 In addition, ICS treatment has been shown to effectively alleviate inflammation mediators and recover innate immune responses, such as surfactant protein D.31 Our findings revealed the clinical benefits of ICS treatment in patients with COPD by improving lung function and relieving symptoms, especially with higher doses of ICS.

The GOLD guidelines for the management of stable COPD strongly suggest that ICS regimens combined with a LABA should be prescribed for patients with group C, D, and/or frequent exacerbations.14,15 However, many case-controlled or retrospectively based studies have reported that ICS-containing regimens are an independent risk factor for an increased incidence of pneumonia,16–18,32–35 although other studies have reported a similar incidence of pneumonia between patients using MD and HD ICS treatment.25 Previous prospective studies had also shown that the annual incidence of pneumonia was no different whether using MD fluticasone (500 µg/day, 7%)36–37 or HD fluticasone (1,000 µg/day, 7%).19 We also found no increased incidence of pneumonia with either a MD or HD ICS in this prospective study (0.08 versus 0.10 [incidence per patient per year]). The major problem for these contradictory results might have arisen from the methodology of pneumonia diagnosis, or differentiation between pneumonia or virus infection-related acute exacerbation in COPD patients. For diagnosis of pneumonia, chest radiograph and sputum studies were important. Therefore, overdiagnosis of the incidence of pneumonia might exist from previous retrospective or case-controlled studies. If the development of pneumonia is not related to the dosage of ICS, then utilizing high doses of ICS in patients with COPD could be a preferable strategy, due to increased benefits and fewer harmful effects.

The rate of pneumonia-related COPD mortality has yet to be clarified. Recent studies have reported that the use of ICS in patients with COPD is associated with a dose-related increase in the risk of pneumonia-related mortality.18,32,33 However, the results of our study do not support these findings, and evidence from randomized trials has also shown that a higher incidence of pneumonia is not associated with pneumonia-induced mortality or overall mortality.19,24,18,39 In summary, a higher dose of ICS dose seems to be a safe strategy to improve current COPD treatment.

Several recent studies have documented an increased risk of tuberculosis in patients with COPD using ICS.40,41 However, in the current prospective study, no patients were diagnosed with pulmonary tuberculosis. The causal relationship between the incidence of tuberculosis and ICS usage should be further elucidated in large population-based prospective studies.
A previous study reported that patients using ICS for asthma or COPD had a 34% increase in the development of diabetes mellitus; however, other case-controlled studies did not support this finding. In the current study, we did not find an increased incidence of hyperglycemia episodes or newly diagnosed cases of diabetes mellitus. Whether the dosage of ICS has an influence on glucose metabolism is still controversial, and further studies are needed to explore the relationship and mechanisms in depth.

The pneumonia rate (per patient per year) was 0.08 in our study. This is similar to that found in the TORCH (TOwards a Revolution in COPD Health) study (0.07). The annual rate of exacerbation was 0.16 in the HD group and 0.34 in the MD group in the study, which is lower than those observed in previous studies (TORCH, 0.85; TRISTAN [TRial of Inhaled STeroids ANd long-acting β2 agonists], 0.97). The reasons why the exacerbation rate was lower may have been a high proportion of previous treatment with a long-acting β2 agonist, long-acting anticholinergic and inhaled corticosteroid, and better lung function before the commencement of the study (FEV$_1$ 46%–47% of predicted in this study; TORCH, 43%–44%; TRISTAN, 44%–45%; ISOLDE [Inhaled Steroids in Obstructive Lung Disease in Europe]). In addition, 12% of enrolled patients had an FEV$_1$ of more than 60% in this study.

There are a number of limitations to this study. First, we did not evaluate extrapulmonary side effects, such as osteoporosis severity or the development of cardiovascular events. Second, the airway pathophysiological mechanism for bacterial colorization and inflammatory cell recruitment after ICS treatment was not evaluated. Third, this was not a double-blinded study, and this may have biased the results. However, objective measurements, such as pneumonia development by chest-radiography and lung-function tests were analyzed to minimize such bias. Fourth, the present study was not find an increased incidence of hyperglycemia episodes or newly diagnosed cases of diabetes mellitus. Whether the dosage of ICS has an influence on glucose metabolism is still controversial, and further studies are needed to explore the relationship and mechanisms in depth.

In conclusion, COPD patients treated with HD ICS showed improved lung-function status, decreased frequency of exacerbations, and greater symptom relief compared with those treated with MD ICS. Furthermore, no significant increase in the incidence of the development of pneumonia was noted, especially among those using HD ICS. This is the first prospective study to compare MD and HD ICS treatment in the effectiveness of COPD treatment, and to help determine the appropriate dose for an anti-inflammation response in patients with COPD.

**Author contributions**
All authors contributed to the study, design, writing and revision of the paper.

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**Disclosure**
The authors report no conflicts of interest in this work.

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