Efficacy and Safety of Formoterol in Japanese Patients with COPD

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Abstract

Objective This study evaluated the efficacy and safety of the formoterol Turbuhaler at dosages of 4.5, 9 and 18 μg bid compared with placebo in Japanese patients with COPD.

Methods In this randomized, double-blind, placebo-controlled, multicenter study, 36 patients with a pre-bronchodilator FEV1 value within 40 to 70% of the predicted value were randomized to receive formoterol at doses of 4.5, 9, and 18 μg bid, and placebo, for 1 week in a crossover fashion.

Results The primary outcome variable, one hour post-dose FEV1 on the last day of the one week treatment period, was significantly higher for all formoterol dosages compared with placebo (p<0.001 for all doses); adjusted g-means for formoterol 4.5, 9 and 18 μg bid, and placebo, were 1.510 L, 1.491 L, 1.520 L and 1.342 L, respectively. All three dosages of formoterol also provided significantly better improvements than placebo in the secondary variables FVC, inspiratory capacity (IC) and morning and evening PEF. Results for IC and PEF indicated a trend towards a larger improvement at higher dosages.

Conclusion Treatment with formoterol at dosages of 4.5, 9 and 18 μg bid showed significantly superior effects to placebo on FEV1, in Japanese patients with COPD. The results for some of the secondary variables (IC and PEF) indicated a trend towards larger improvements at higher dosages. All dosages of formoterol were well tolerated in Japanese patients.

Key words: formoterol, Japanese, inspiratory capacity, COPD

(DOI: 10.2169/internalmedicine.47.0494)

Introduction

COPD is a disease state characterized by the presence of chronic airflow limitation that progresses slowly over a period of years and is not fully reversible (1). A systematic review and meta-analysis estimated the global prevalence of physiologically defined COPD in adults aged ≥40 years to be approximately 9-10% (2). In Japan, a spirometry-based study conducted in the year 2000 conservatively estimated the prevalence of COPD to be at least 8.6% in Japanese people aged ≥40 years (3).

Although much of the damage is irreversible at clinical presentation, there are treatments available to improve symptoms, quality of life and functional ability in patients with COPD (4-7). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, bronchodilators such as long-acting β2-agonists are central to the symptomatic management of COPD (1). The long-acting β2-agonist formoterol has a duration of effect of ≥12 hours and an onset of action within three minutes in patients with asthma (8), properties which would be beneficial in COPD.

Received for publication August 3, 2007; Accepted for publication November 4, 2007
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patients, especially those who need frequent treatment and those with nocturnal symptoms.

In Europe, studies have shown formoterol to have beneficial effects at dosages of 4.5, 9 and 18 μg twice daily (bid) in patients with COPD (9, 10). However, the effects of formoterol on lung functions and symptoms have never been investigated in Japanese patients with COPD. The aim of this randomized, controlled, crossover study was to evaluate the efficacy and safety of three dosages of formoterol (4.5, 9 and 18 μg bid), compared with placebo, for 7 days in Japanese patients with COPD.

Methods

Patients

Patients aged ≥40 years were eligible for inclusion in the study if they had a clinical diagnosis of COPD with symptoms for at least 1 year, and were a current- or ex-smoker with a smoking history of at least 10 pack years. At randomization, their pre-bronchodilator FEV1/FVVC had to be less than 70%, and their pre-bronchodilator FEV1 had to be 40-70% of the predicted value.

Patients were excluded if they had a history of bronchial asthma or allergic rhinitis, any clinically significant respiratory tract disorders other than COPD, significant or unstable ischemic heart disease or any other relevant cardiovascular disorder, or any other significant disease or disorder that might put them at risk or influence the study results or their ability to participate. Other exclusion criteria included an exacerbation of COPD during the run-in period or within 30 days prior to enrollment requiring medical intervention, use of corticosteroids within 30 days of enrollment, use of β-blockers, and regular use of oxygen therapy.

This study was performed in accordance with the ethical principals of Good Clinical Practice and the Declaration of Helsinki. An Institutional Review Board approved the study protocol and all patients gave written informed consent before any procedures were initiated.

Study design and treatments

This randomized, double-blind, placebo-controlled, crossover study took place in 9 centers in Japan. Following a 1-week run-in period, patients were randomized to receive each of the following treatments for 1 week, with a 1-week washout period between treatments: formoterol Turbuhaler® [Oxis® Turbuhaler®; AstraZeneca, Liquid Production, Sweden] 4.5 μg bid, 9 μg bid, 18 μg bid, and placebo. Patients visited the clinic at enrollment (visit 1), and the first and last day of each treatment period (visits 2-9).

Patients were allowed salbutamol pressurized metered dose inhaler (pMDI) as rescue medication. They were not allowed the following medications during the study: inhaled, parenteral, oral and nebulized glucocorticosteroids; inhaled short-acting β-agonists other than salbutamol pMDI; inhaled long-acting β2-agonists other than the study drug and transdermal β2-agonist; oral β-agonists; inhaled and oral anticholinergics; medicines containing ephedrine; xanthine derivatives; leukotriene antagonists; antihistamines.

Patients were randomized strictly sequentially as they became eligible for randomization. The investigational product was allocated by a third party i.e., the person responsible for randomization of the investigational product. Treatment codes, indicating the allocated treatment for each patient, were available for emergency situations.

Assessments

The primary efficacy endpoint was 1 hour post-dose FEV1. The secondary endpoints were 1 hour post-dose FVC, 1 hour post-dose inspiratory capacity (IC), average value of morning and evening PEF during the treatment period, and number of as-needed short-acting β2-agonist inhalations during the treatment period.

Lung function tests were performed to measure FEV1 and FVC on the first and last day of each treatment period. The same spirometer (Pneumotrac™) was used for each patient throughout the study. FVC measurements were taken three times at short intervals (within 1 minute), and the highest value was assessed. FEV1 values were taken from the FVC curves. The IC values were calculated from the slow VC curve, which is the total lung capacity minus the functional residual capacity. For the lung function tests, at least three technically satisfactory FVC maneuvers were performed, with a difference between highest and second highest FEV1 of not more than 5% or 0.1 L, and the highest value in the three records was recorded. A maximum of eight maneuvers was performed to meet the reproducibility criteria. If the reproducibility criteria could not be met within eight maneuvers, the highest value was recorded. At least three technically satisfactory slow VC maneuvers were also performed. The average value of the three records was recorded as the IC value.

The patients used diaries to record morning and evening PEF and the use of rescue medication. Each patient was issued a Mini-Wright™ peak flow meter and they were instructed in its use.

In order to collect information on adverse events, patients were asked a standard question at each visit about whether they had experienced any health problems since the last visit. Hematology, clinical chemistry and urine tests were performed at enrollment and visit 9 or the time of withdrawal from the study, and routine physical examination and measurement of vital signs were performed at visits 1 to 9.

Statistical analysis

An improvement of 4% of predicted in FEV1 compared with placebo has been regarded as clinically meaningful (11), and corresponds to an increase in mean FEV1 of 8% compared with placebo in the target population in this study. Hence, a total of 29 patients completing all study treatments was regarded as necessary to detect the 8% difference with the power of 80% and a one-sided 2.5% significance level.
assuming that the standard deviation of log-transformed 
FEV₁ was 0.10 (9). Allowing for withdrawals, a total of 37 
patients was the target sample size for randomization in this 
study.

The primary analysis set for efficacy was the full analysis 
set (FAS). Statistical analysis was conducted using SAS ver-
sion 8.2. For FEV₁, comparisons of each of the three-
formoterol dosages with placebo were performed using the 
multiplicative model of Analysis of Variance (ANOVA) in-
cluding patient as a random effect and period and treatment 
as fixed factors. A two-sided 5% significance level was 
used. In addition to p-value, the estimate and 95% confi-
dence interval for the mean difference between each of the 
formoterol dosages and placebo were computed from the 
model. Comparisons between all pairs of formoterol dosages 
were performed using the same model. FVC and IC were 
analyzed by the same methods as FEV₁.

For morning and evening PEF, comparisons between each 
of the formoterol dosages and placebo, and between all pairs 
of formoterol dosages, were performed using an additive 
ANOVA model including patient as a random effect, and pe-
riod and treatment as fixed factors. The mean number of as-
needed short-acting β₂-agonist inhalations (daytime, night-
time and total) was compared between the formoterol dos-
ages and placebo, and between each of the formoterol dos-
ages, in a similar way as morning PEF.

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**Results**

**Patient characteristics**

A total of 69 clinically diagnosed COPD patients were 
screened in the study. Of these, 32 showed an FEV₁ of more 
than 70% of predicted and one had an adverse event prior to 
randomization. Subsequently, 36 patients were randomized 
to treatment. Figure 1 shows the flow of patients through 
the study. After randomization, one patient was withdrawn 
during the washout period after receiving formoterol at a 
dosage of 18 µg bid. All randomized patients were included 
in the safety analysis set and the FAS for the 9 and 18 µg 
bid dosages of formoterol, while 35 patients were included 
in the FAS for placebo and the 4.5 µg bid dosage due to 
premature discontinuation in one patient. Key demographic 
and baseline characteristics of the randomized patients are 
shown in Table 1.

**Clinical efficacy**

**Primary variable**

On the first day of each treatment period, pre-dose FEV₁ 
values taken for placebo and formoterol 4.5 µg bid, 9 µg bid 
and 18 µg bid, were 1.386 L, 1.421 L, 1.389 L and 1.406 L, 
respectively (Table 2). There was no significant difference in 
pre-dose FEV₁ values among the four groups. On the last
day of treatment, post-dose FEV₁ was significantly higher for all formoterol dosages compared with placebo (p<0.001 for all dosages). No significant differences in 1 hour post-dose FEV₁ values were observed among the three-formoterol dosages (Fig. 2A).

**Secondary variables**

The values of post-dose FVC and IC were shown in Table 2. Post-dose FVC on the last day of treatment was significantly higher for all formoterol dosages compared with placebo (p < 0.001), with no significant differences in 1 hour post-dose FVC values between the three-formoterol dosages (Fig. 2B).

Post-dose IC on the last day of treatment was significantly higher for all formoterol dosages compared with placebo. A slight increase in the estimate values of the ratio to placebo was observed as the formoterol dosage increased. Mean 1 hour post-dose IC for the 18 μg bid dosage was significantly higher than for 4.5 μg bid (p<0.05) (Fig. 2C).

The values of morning and evening PEF were shown in Table 3. Mean morning PEF was significantly higher for all of the formoterol dosages compared with placebo (p<0.001). The difference from placebo at the 18 μg bid dosage was significantly higher than for the 4.5 μg bid (p<0.05) and 9 μg bid (p<0.01) dosages (Fig. 3A).

Mean evening PEF was also significantly higher for all formoterol dosages than placebo (p<0.001). Increasing formoterol dosages were associated with increased differences relative to placebo. Mean evening PEF for the 18 μg bid dosage was significantly higher than for the 4.5 μg bid (p = 0.01) and 9 μg bid (p<0.05) dosages (Fig. 3B).

The number of as-needed short-acting β₂-agonist inhalations (as day total) was significantly lower at the 4.5 and 9 μg bid formoterol dosages compared with placebo (p = 0.007 and 0.031, respectively), but not the 18 μg bid dosage (p=0.142). There were no significant differences among the three formoterol dosages.

**Tolerability**

A total of seven adverse events were reported in six patients (Table 4). Reported adverse events were of mild intensity. No patients withdrew from the study due to an adverse event and there were no deaths, serious adverse events or other significant adverse events identified. The most common adverse event was nasopharyngitis, which was reported in four patients (one patient at the 4.5 and 9 μg bid dosages and two at 18 μg bid).

**Discussion**

This study compared treatment with formoterol at dosages of 4.5, 9 and 18 μg, bid, with placebo, for 7 days in Japanese patients with COPD. These patients had a baseline FEV₁ between 40 and 70% of predicted values, and were classified as having moderate to severe COPD according to the GOLD guidelines (1). The primary efficacy analysis showed all formoterol dosages to be significantly superior to placebo in improving FEV₁, in these patients, with no significant differences among the three dosages.

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**Table 1. Baseline Characteristics of Patients**

<table>
<thead>
<tr>
<th>Sex; M/F [n (%)]</th>
<th>34 (94.4) / 2 (5.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>70.2 ± 10.1</td>
</tr>
<tr>
<td>Race; Oriental [n (%)]</td>
<td>36 (100)</td>
</tr>
<tr>
<td>Smoking; pack year [n (%)]</td>
<td></td>
</tr>
<tr>
<td>10 - 20</td>
<td>2 (5.6)</td>
</tr>
<tr>
<td>21 - 30</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>31 (86.1)</td>
</tr>
<tr>
<td>FEV₁ [L]</td>
<td>1.43 ± 0.39</td>
</tr>
<tr>
<td>FEV₁ [% predicted]</td>
<td>52.3 ± 7.90</td>
</tr>
<tr>
<td>FEV₁/FVC [%]</td>
<td>49.0 ± 7.30</td>
</tr>
<tr>
<td>FEV₁ reversibility [%]</td>
<td>10.1 ± 8.50</td>
</tr>
</tbody>
</table>

*Abbreviations: FEV₁: forced expiratory volume in one second; FVC: forced vital capacity*
Formoterol also provided significant improvements relative to placebo in the secondary efficacy variables including FVC, IC and morning/evening PEF. Results for IC and morning/evening PEF showed a trend towards greater improvements at higher dosages; the improvement observed at 18 μg bid was significantly superior to that of 4.5 μg bid for IC, and was significantly superior to that at both of the lower dosages for PEF.

Formoterol 4.5 and 9 μg bid reduced the number of as-needed inhalations of short-acting β₂-agonists compared with placebo, while the effects of 18 μg bid were not statistically significant in this study. In a European study, formoterol at 9 and 18 μg, but not 4.5 μg bid significantly reduced the number of as-needed medications (10). These results suggest that formoterol may be useful in reducing the need for rescue medication in Japanese patients as well as Caucasian patients.

The GOLD guidelines suggest that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators in patients with COPD (1). Moreover, long-acting β₂-agonist therapy has been suggested as a first-line option for the treatment of patients with COPD who require regular bronchodilator therapy for the management of their symptoms (12-14). It has been shown that long-acting β₂-agonists such as formoterol and salmeterol have ≥12 hours’ duration of effect in COPD patients, with effects lasting overnight with regular use (1).

In the European crossover study it was found that 7 days’ treatment with formoterol at dosages of 4.5, 9 and 18 μg bid was efficacious in patients with COPD (9). This study concluded that all dosages of formoterol, and also ipratropium bromide, significantly improved exercise capacity and FEV₁ compared with placebo in these patients. The authors commented that the effect of formoterol was comparable to that of ipratropium at a dosage of 80 μg three times daily. Aalbers et al. also reported that 12 weeks’ treatment with formoterol at dosages of 4.5, 9, 18 μg bid significantly increased FEV₁, compared with placebo in patients with moderate to severe COPD (10). The results of the present study are compatible with these reports, and this demonstrates that formoterol has a beneficial effect on the reversible element of bronchoconstriction in Japanese patients with COPD.

It has been shown that there is genetic variation in the β₂-adrenergic receptor, and it has been suggested that the frequency of genetic phenotypes varies between ethnic groups (15-18). We have compared our study results to those of two
formoterol studies for COPD in European countries (9, 10). We found no differences between Japanese and Caucasian patients, suggesting that ethnic differences do not affect the efficacy of formoterol.

In the present study, dose-dependent effects of formoterol were observed in IC and PEF but not in FEV₁. IC is volume parameter which reflects lung hyperinflation. In contrast, FEV₁ and PEF are flow parameters which reflect airway resistance and lung elastic recoil. Air trapping leads to hyperinflation, and this may result in a small FEV₁ response and thus underestimation of the beneficial effect of bronchodilator in severe COPD (19). The increased IC by formoterol suggests the improvement in hyperinflation. However, dose-dependent effects of formoterol were also observed in PEF. Therefore, it is unlikely that the volume effect of the formoterol is the sole reason for the dose dependency.

The treatment with formoterol for 1 week at dosages of up to 18 μg bid was well tolerated in Japanese patients in the present study. Reported adverse events were of mild intensity and there were no serious adverse events reported. There did not appear to be any dose-related patterns with regard to the adverse events reported. Again we have compared the study results to those of formoterol studies in European countries and found no difference in the safety profile of formoterol (9, 10). Similarly, other clinical trials in patients with COPD have found formoterol to be generally well tolerated (10, 14, 20). However, concerns have been raised about the cardiovascular safety of inhaled β₂-agonists in general due to the presence in the literature of reports of adverse events in patients with obstructive airway disease (21, 22). A review of the cardiovascular safety of β₂-agonists in patients with obstructive lung disease concluded that these agents must always be used with caution in patients with cardiovascular disease as they may precipitate the concomitant cardiac disease (21).

In conclusion, treatment with formoterol Turbuhaler® at dosages of 4.5, 9 and 18 μg bid provided significantly better improvements than placebo in the primary efficacy variable FEV₁ in Japanese patients with COPD similar to results in Caucasian patients. Results for some secondary variables such as IC and PEF indicated a trend towards larger improvements at higher formoterol dosages. Treatment with formoterol at all dosages was well tolerated and raised no new safety concerns in Japanese patients.

Acknowledgement
This study was financially supported by AstraZeneca. The authors would like to acknowledge T. Kudo and Y. Ozawa of As-

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**Figure 3.** (A) Morning PEF and (B) evening PEF after 1 week of treatment with formoterol 4.5, 9 or 18 μg bid. Data are expressed as adjusted geometric means, and the difference from the value in the placebo group. Error bars were indicated as 95% confidence interval. Abbreviations; PEF: peak expiratory flow; bid: twice daily.

**Table 4.** Numbers of Adverse Events Reported by Patients Receiving Rormoterol 4.5, 9 or 18 g Bid or Placebo (FAS)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=35)</th>
<th>Formoterol 4.5μg (n=35)</th>
<th>Formoterol 9μg (n=36)</th>
<th>Formoterol 18μg (n=36)</th>
<th>Total (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>0 (0)</td>
<td>1 (2.9)</td>
<td>1 (2.8)</td>
<td>2 (5.6)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0 (0)</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Vertigo positional</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Tremor</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.8)</td>
<td>1 (2.8)</td>
</tr>
</tbody>
</table>
traZeneca for their help in statistical analysis and SAS programming. We would also like to acknowledge Rosalind Weinstock for her assistance in preparation and editing of the manuscript.

References