Table 4 Summary of trough, peak and average (AUC_{0-3h}) FVC responses, in the full analysis set. Mean responses are adjusted for effects of patient, period and baseline FVC on Day 1.

	Tiotropium Respimat® 5 μg ($n = 134$)	Tiotropium HandiHaler® 18 μg ($n = 134$)
Trough FVC, L		
Adjusted mean increase, Day 29 minus Day 1 (95% CL)	0.213 (0.186, 0.241)	0.217 (0.190, 0.245)
Difference, Respimat® minus HandiHaler® (95% CL)	−0.004 (−0.044, 0.036)	
p value for difference between inhalers[a]	0.8384	
Peak FVC, Day 1, L		
Adjusted mean response (95% CL)	0.383 (0.359, 0.407)	0.409 (0.386, 0.433)
Difference, Respimat® minus HandiHaler® (95% CL)	−0.026 (−0.060, 0.008)	
p value for difference between inhalers[a]	0.1278	
Peak FVC, Day 29, L		
Adjusted mean response (95% CL)	0.424 (0.398, 0.450)	0.411 (0.385, 0.437)
Difference, Respimat® minus HandiHaler® (95% CL)	0.013 (−0.024, 0.049)	
p value for difference between inhalers[a]	0.4973	
FVC AUC_{0-3h}, Day 1, L		
Adjusted mean response (95% CL)	0.250 (0.230, 0.269)	0.272 (0.252, 0.291)
Difference, Respimat® minus HandiHaler® (95% CL)	−0.022 (−0.050, 0.006)	
p value for difference between inhalers[a]	0.1219	
FVC AUC_{0-3h}, Day 29, L		
Adjusted mean response (95% CL)	0.326 (0.303, 0.350)	0.316 (0.292, 0.339)
Difference, Respimat® minus HandiHaler® (95% CL)	0.010 (−0.023, 0.044)	
p value for difference between inhalers[a]	0.5414	

Abbreviations: CL, confidence limits; SE, standard error.
[a] Two-sided ANCOVA.

reported from the pooled crossover results in European and US patients.[19] In our study, nasopharyngitis, COPD exacerbation and dry mouth were the three most common adverse events, which is consistent with previous experience from clinical trials of tiotropium.[22]

Taken together, the results of our study show that the Respimat® inhaler is a more efficient inhaler than HandiHaler®. A daily dose of only 5 μg produces similar efficacy and pharmacokinetics to a dose more than threefold higher from HandiHaler®, and tolerability and safety profiles are similar. Deposition studies have shown that a higher proportion of the dose emitted from the Respimat® inhaler is delivered to the lungs compared with pMDIs and a multidose DPI.[16,17] In a clinical trial of COPD patients, this allowed the nominal dose of bronchodilator from a pMDI to be reduced by 50% while maintaining efficacy and safety.[23]

Although the protocol of our study allowed inclusion of men and women, the full analysis set included only 3 women.

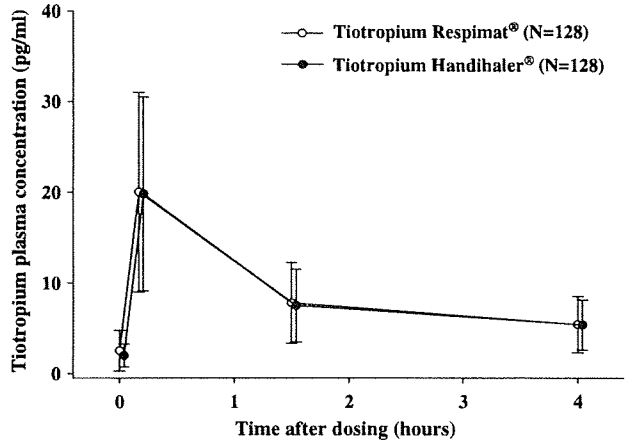

Figure 3 Change in arithmetic mean plasma concentrations of tiotropium after dosing on Day 29. Error bars show standard deviations.

Table 5 Summary of adverse events during study. Events that occurred in at least 2% of patients in either group are listed by preferred term.

Number of patients reporting (*n*, %)	Tiotropium Respimat®	Tiotropium HandiHaler®
All patients	147 (100)	147 (100)
Any adverse event	45 (30.6)	41 (27.9)
Nasopharyngitis	13 (8.8)	9 (6.1)
COPD exacerbation	6 (4.1)	4 (2.7)
Dry mouth	2 (1.4)	3 (2.0)
Diarrhoea	1 (0.7)	3 (2.0)
Rash	0 (0)	3 (2.0)
Any drug-related adverse event[a]	4 (2.7)	8 (5.4)
Adverse events leading to discontinuation	1 (0.7)	2 (1.4)
Serious adverse events	4 (2.7)	6 (4.1)

[a] As judged by the investigator.

This is not unexpected, firstly because the smoking rate in Japan is much higher in men than in women, and secondly because Japanese women are generally reluctant to enrol in clinical trials, not only in COPD but also in other diseases. Although placebo inhalers were used in our study to conceal the identity of the active inhaler, there was no all-placebo arm in the study, in contrast to the Respimat®–HandiHaler® comparison studies in Europe and US patients. In that analysis however, all three active treatment arms were found to be associated with significantly better lung function than placebo.[19]

In conclusion, tiotropium Respimat® 5 μg was shown to have similar efficacy and safety as tiotropium HandiHaler® 18 μg when used for the treatment of Japanese patients with COPD, and the 90% confidence intervals of AUC and Ae ratios (Respimat®: HandiHaler®) lay within the interval of 80–125%.

Acknowledgements

We acknowledge the following investigators who participated in this trial: H Taniguchi, S Matsumoto (Aichi); K Miura, K Kimura (Akita); N Kaneko (Chiba); H Aizawa, T Kawayama (Fukuoka); Kyong-Yob Min (Hyogo); H Nakamura, S Oishi, A Nomura, K Sekizawa (Ibaraki); K Yamauchi (Iwate); H Takahashi (Kanagawa); S Muro (Kyoto); H Ogawa, M Miura, T Takahashi (Miyagi); K Fujimoto, K Kubo (Nagano); H Ishihara, H Kita, K Hirata, M Kato, R Maekura, Y Inoue, Y Tohda (Osaka); K Takahashi, K Asano, K Kida (Tokyo); Y Minakata (Wakayama). Medical writing support for this article was provided by Roger Nutter at Lexeme, Chester, UK, and funding for this support was provided by Boehringer Ingelheim. The study was funded by Boehringer Ingelheim.

Conflict of interest statement

M.I. has previously served on scientific advisory boards of GlaxoSmithKline KK, Nippon Boehringer Ingelheim, Novartis Pharma KK and AstraZeneca KK. He has received lecture fees from GlaxoSmithKline KK, AstraZeneca KK and Nippon Boehringer Ingelheim and unrestricted grants from GlaxoSmithKine KK and Nippon Boehringer Ingelheim. TF is an employee of Nippon Boehringer Ingelheim, the sponsors of the trial, and contributed to study design, data interpretation, manuscript review and the collective decision to submit the manuscript for publication. Y.F. has previously served on scientific advisory boards of GlaxoSmithKline KK, Nippon Boehringer Ingelheim, Novartis Pharma KK, AstraZeneca KK, Kyorin KK, Abbot Japan and Ohtsuka pharma. He has received lecture fees from GlaxoSmithKline KK, AstraZeneca KK, Nippon Boehringer Ingelheim, Abbot Japan and Ohtsuka pharma and unrestricted grants from Nippon Boehringer Ingelheim.

References

1. Tashkin D, Kesten S. Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. *Chest* 2003;**123**:1441–9.
2. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005;**143**:317–26.
3. Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. *Thorax* 2006;**61**:854–62.
4. Tashkin DP, Celli B, Senn S, et al. for UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;**359**:1543–54.
5. van Noord JA, Bantje TA, Eland ME, Korducki L, Cornelissen PJ. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax* 2000;**55**:289–94.
6. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002;**122**:47–55.
7. Vincken W, van Noord JA, Greefhorst AP, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002;**19**:209–16.
8. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;**19**:217–24.
9. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003;**58**: 399–404.
10. Dusser D, Bravo ML, Iacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. *Eur Respir J* 2006;**27**:547–55.
11. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. *Chest* 2003; **124**:1743–8.
12. O'Donnell DE, Flüge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;**23**:832–40.
13. Casaburi R, Kukafka D, Cooper CB, Witek Jr TJ, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005;**127**:809–17.
14. Zierenberg B. Optimizing the in vitro performance of Respimat. *J Aerosol Med* 1999;**1**(Suppl. 12):S19–24.

15. Hochrainer D, Hölz H, Kreher C, Scaffidi L, Spallek M, Wachtel H. Comparison of the aerosol velocity and spray duration of Respimat® Soft Mist Inhaler™ and pressurized metered dose inhalers. *J Aerosol Med* 2005;**18**:273–82.
16. Newman SP. Use of gamma scintigraphy to evaluate the performance of new inhalers. *J Aerosol Med* 1999;**12**(Suppl. 1): S25–31.
17. Pitcairn G, Reader S, Pavia D, Newman S. Deposition of corticosteroid aerosol in the human lung by Respimat® Soft Mist™ Inhaler compared to deposition by metered dose inhaler or by Turbuhaler® dry powder inhaler. *J Aerosol Med* 2005;**18**:264–72.
18. Caillaud D, Le Merre C, Martinat Y, Aguilaniu B, Pavia D. A dose-ranging study of tiotropium delivered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2007;**2**:559–65.
19. van Noord JA, Cornelissen PJG, Aumann J-L, Platz J, Mueller A, Fogarty C. The efficacy of tiotropium administered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. *Respir Med* 2009;**103**:22–9.
20. Pulmonary Physiology Specialist Committee of the Japanese Respiratory Society. Report: standard values for spirometry and partial pressure of blood gas [in Japanese]. *J Jpn Respir Soc* 2001;**39**:1–17.
21. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Available from, http://www.goldcopd.org; 2007 [accessed 21 August 2008].
22. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest* 2006;**130**:1695–703.
23. Kilfeather SA, Ponitz HH, Beck E, et al. Improved delivery of ipratropium bromide/fenoterol from Respimat® Soft Mist™ Inhaler in patients with COPD. *Respir Med* 2004;**98**: 387–97.

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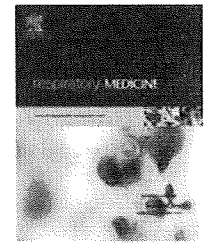

Additive effects of transdermal tulobuterol to inhaled tiotropium in patients with COPD

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Received 20 May 2009; accepted 19 September 2009
Available online 28 October 2009

KEYWORDS
Chronic obstructive pulmonary disease;
Inhaled tiotropium;
Pulmonary function;
Quality of life;
Transdermal tulobuterol

Summary
Background: The current mainstream treatment for COPD is bronchodilators alone or in combination. The effects of a β_2-agonist, tulobuterol, administered transdermally, have been reported to last for 24 h. However, there are no reports on the efficacy of tulobuterol combined with an anticholinergic. In this study, we investigated the efficacy and safety of transdermal tulobuterol combined with inhaled tiotropium in COPD.
Methods: After a 2-week run-in period, 103 stable COPD patients aged ≥40 years were randomized into two groups: inhaled tiotropium (18 μg, Tio group) or transdermal tulobuterol (2 mg) combined with inhaled tiotropium (18 μg, Tio + Tulo group) for 8 weeks. Primary endpoints were pulmonary function and severity of dyspnea. The St. George's Respiratory Questionaire (SGRQ) score was a secondary endpoint.
Results: In both groups, FEV_1 and FVC as well as dyspnea improved significantly after 8 weeks. In a comparison of both groups, percentage changes in IC and morning and evening peak expiratory flow were significantly greater in the Tio + Tulo group than in the Tio group. In addition, significant improvement in SGRQ score was observed in the Tio + Tulo group only. The risk of

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2009.09.012

adverse events related to the study drugs was not increased.
Conclusion: In COPD patients, additional administration of transdermal tulobuterol to inhaled tiotropium produced significant benefits in dyspnea and SGRQ score as well as pulmonary function. These benefits may be due to a reduction in pulmonary hyperinflation resulting from improvement of peripheral airflow obstruction through tulobuterol via the systemic circulation.

Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease that occurs as a result of inhalation of harmful particles, such as those in cigarette smoke. There is some concern that the number of COPD patients will increase with the aging of the population. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends the use of long-acting bronchodilators, such as anticholinergics, β_2-agonists, and methylxanthines, for the management of stable COPD patients.[1] In addition, the combined use of bronchodilators with different mechanisms of action results in greater potency and fewer adverse effects, and is therefore recommended rather than increasing the dose of a single agent when symptoms are not well controlled by monotherapy.

Tiotropium, which has been available in Japan since 2004, is an anticholinergic that is inhaled once daily. Its efficacy has been demonstrated in large-scale clinical studies.[2–10] In a recent study in which the use of all drugs for COPD treatment except inhaled anticholinergics was allowed, the efficacy and safety of tiotropium were investigated in 5993 COPD patients over 4 years, in comparison with a placebo. In this study, tiotropium was demonstrated to improve pulmonary function and quality of life (QOL), and to reduce the risk of exacerbations in COPD and related hospitalizations.[11] Based on such evidence, inhaled tiotropium is regarded as a new therapeutic option for COPD in addition to β_2-agonists and methylxanthines.

Transdermal tulobuterol, which is frequently used for COPD treatment, was developed in Japan as the world's first long-acting β_2-agonist in a patch formulation. This formulation of tulobuterol was designed to maintain drug levels at constant effective concentrations over a 24-h period when applied once daily.[12,13] Administered this way, tulobuterol exerts its effect through the systemic circulation and provides a lower maximum blood concentration, resulting in fewer systemic adverse effects, such as palpitation and tremor, than oral formulations. In addition, transdermal tulobuterol avoids the first-pass effect and is expected to cause fewer adverse effects, such as gastrointestinal symptoms. To date, transdermal tulobuterol has been launched in Japan, Korea, and China. The efficacy of this drug in COPD patients was investigated in a randomized comparative study using inhaled salmeterol, which is used for the treatment of COPD.[14] That study demonstrated that, compared with inhaled salmeterol, transdermal tulobuterol has an equivalent effect of improving pulmonary function and is significantly superior in improving sleep scores and QOL.[14]

These findings suggest that the combined use of two long-acting once-daily bronchodilators, transdermal tulobuterol and inhaled tiotropium, with different mechanisms of action, is an excellent treatment for COPD patients whose symptoms are not well controlled by monotherapy. However, there are few reports on the efficacy and safety of combination therapy with these two drugs, and the benefits of such a combination therapy have not been fully confirmed. Therefore, we conducted a clinical study to verify the efficacy and safety of the combined use of transdermal tulobuterol and inhaled tiotropium in COPD patients.

Methods

Subjects

The study was conducted in patients aged $\geq$40 years with a clinical diagnosis of COPD who had the following conditions: FEV_1/FVC <70% 15–60 min after inhalation of a short-acting β_2-agonist, with FEV_1 30–80% of the predicted value, in pulmonary function tests performed during the screening period; current or past smoking history; and relatively stable condition with persistent dyspnea. All subjects were out-patients. Their status did not change during the study period, and they remained out-patients. Before the implementation of the study, the study objectives were explained to patients and those who provided informed consent to participate in the study were enrolled.

The following patients were excluded: patients whose major symptom was bronchial asthma; patients on treatment with oral steroids; patients with respiratory failure on home oxygen therapy; patients with previous hypersensitivity to tulobuterol; patients with skin diseases, such as atopic dermatitis, who are considered unsuitable for treatment with transdermal tulobuterol; patients with concurrent hyperthyroidism, hypertension, heart disease, or diabetes mellitus, who are considered unsuitable for treatment with β_2-agonists; patients with glaucoma; patients with dysuria associated with, for example, benign prostatic hyperplasia; patients with previous hypersensitivity to atropine and related substances or to tiotropium; patients who were or may have been pregnant, were breastfeeding, or intended to become pregnant during the study period; and other patients judged ineligible for the present clinical study by the attending physician.

The study complied with the Declaration of Helsinki of the World Medical Association. The protocol was approved by the ethics committees of the institutions involved.

Study design

The study was conducted as a multicenter parallel-group comparison study. The assignment of subjects was performed using a randomized subject assignment list prepared based on a random number table by a central registration center, a third party. After a 2-week run-in period, patients were randomized to either a group receiving inhaled tiotropium (one capsule of 18 μg) (the Tio group) or a group receiving transdermal tulobuterol (2 mg) in combination with inhaled tiotropium (one capsule of 18 μg) (the Tio + Tulo group), and treated for 8 weeks (Fig. 1). Tiotropium was inhaled using a designated inhalation device (HandiHaler), once daily between 7 a.m. and 9 a.m. Transdermal tulobuterol was applied to the chest, back, or upper arm, once daily, after bathing and before going to bed, by about 8 p.m.

Throughout the study period, the use of additional bronchodilators was not allowed, but the use of short-acting inhaled β_2-agonists was allowed as necessary. A 2-week washout period was set for patients already on treatment with a long-acting β_2-agonist or tiotropium. For patients who were on treatment with theophyllines, inhaled steroids, antiallergic agents, antihistamines, antitussives, expectorants, or anti-inflammatory enzyme preparations from before the start of the study, the concomitant use of these drugs was allowed. However, in principle, the dose and dosing regimen were not to be changed during the study period.

Pulmonary function tests and QOL assessment

The primary endpoints were pulmonary function and severity of dyspnea. For pulmonary function, spirometry was performed to determine FVC, FEV_1, $\%FEV_1$, and IC at the start and end of study treatment. Spirometry was performed and measured between 9:00 am and noon. In addition, the morning and evening peak expiratory flows (PEFs) were measured using a peak flow meter (Mini-Wright, ATS scale; Matsuyoshi) every day. Trough values of peak flows were measured on getting up (before tiotropium inhalation) and before going to bed (before tulobuterol application). Severity of dyspnea was evaluated using the Medical Research Council dyspnea scale at the start and end of study treatment. As a secondary endpoint, QOL was evaluated using the St. George's Respiratory Questionnaire (SGRQ), which is a disease-specific QOL questionnaire, at the start and end of study treatment. In addition, for safety, adverse events and abnormal laboratory values were evaluated.

Statistical procedures

Data are expressed as means ± SD. For pulmonary function indices, comparison of mean changes from baseline was performed using the paired *t*-test, and between-group comparisons of percentage changes from baseline were performed using the Wilcoxon rank sum test. For PEFs, comparisons of percentage changes from baseline were performed using the Wilcoxon signed rank test, and between-group comparisons of percentage changes from baseline were performed using the Wilcoxon rank sum test. For QOL scores, comparison of mean changes from baseline were performed using the paired *t*-test, and between-group comparisons of changes from baseline were performed using Welch's *t*-test. The significance level was set at less than 5%.

Results

Subjects analyzed

One hundred and three patients were enrolled from 26 institutions in Japan. Of these, 50 and 53 patients were randomly assigned to the Tio group and the Tio + Tulo group, respectively. During the study period, 11 patients from the Tio group and nine patients from the Tio + Tulo group were withdrawn from the study. Reasons for withdrawal of these patients were failure to meet the pulmonary function test criteria (three of the Tio group and three of the Tio + Tulo group), no data available for the screening period (one of the Tio group), treatment violation during the screening period (two of the Tio group and two of the Tio + Tulo group), treatment non-compliance during the study period (one of the Tio group and one of the Tio + Tulo group), and treatment discontinuation owing to, for example, adverse drug reactions (four of the Tio group and three of the Tio + Tulo group). As a result, 83 patients (39 patients from the Tio group and 44 patients from the Tio + Tulo group) were evaluated for efficacy (Fig. 2).

The characteristics of the 83 subjects evaluated for efficacy are shown in Table 1. No differences between the treatment groups were noted in sex, age, height, weight, or smoking status. In addition, although theophyllines, expectorants, and short-acting β_2-agonists were used as

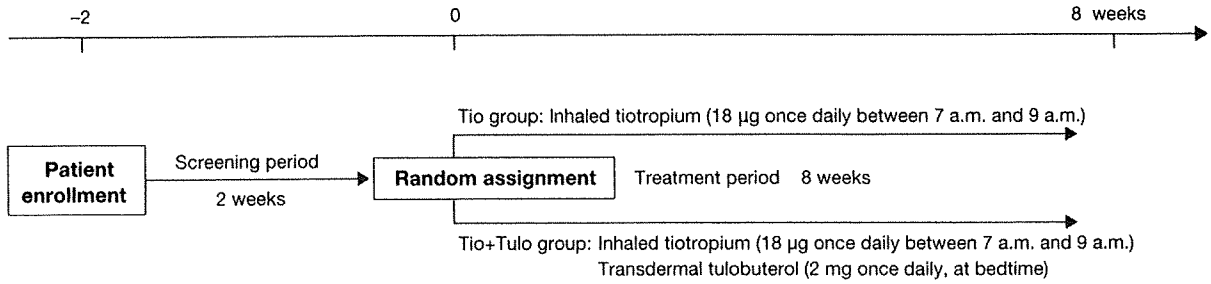

Figure 1 Study protocol.

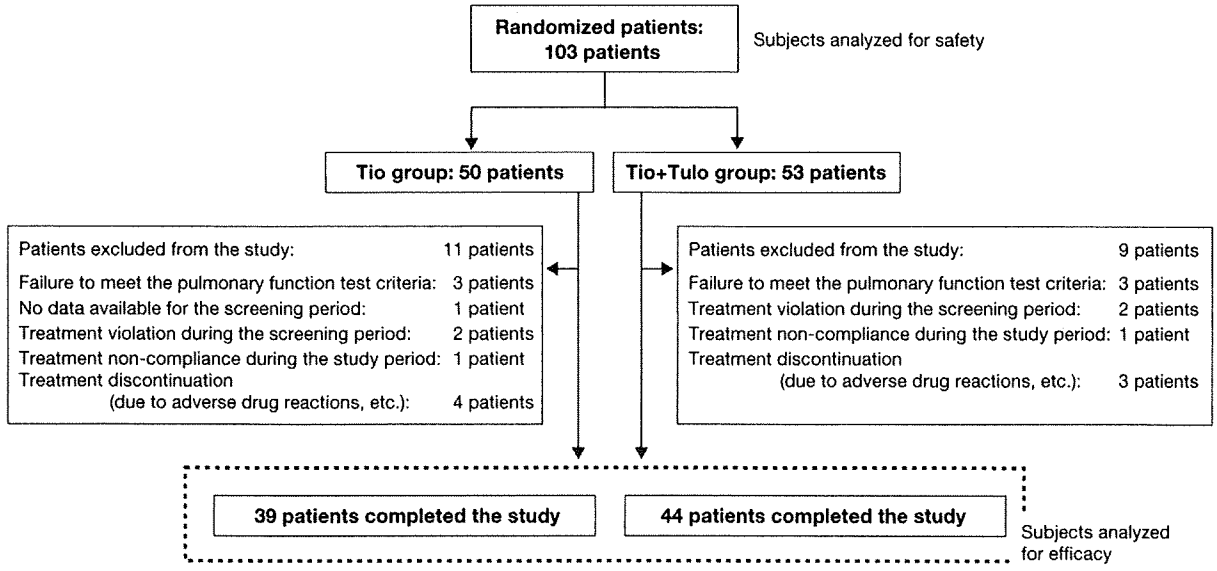

Figure 2 Allocation to treatment groups and status at follow-up.

concomitant drugs, no difference in the proportion of subjects receiving concomitant drugs was noted between the treatment groups. Regarding pulmonary function, FEV_1 and $\%FEV_1$ tended to be higher in the Tio group. Regarding QOL scores, the symptoms, impact, and total SGRQ scores tended to be better in the Tio group.

Efficacy

Changes in pulmonary function indices assessed by spirometry before and after treatment are shown in Table 2. After 8 weeks of treatment, mean FVC, FEV_1, and $\%FEV_1$ values improved significantly from baseline in both groups ($P < 0.001$ for each), whereas a significant improvement in IC was observed in the Tio + Tulo group only ($P < 0.05$).

In a between-group comparison of pulmonary function indices, the percentage changes in FVC and FEV_1 were not significantly different between the two treatment groups. For the percentage change in IC, a significant improvement was observed in the Tio + Tulo group compared with the Tio group ($P < 0.05$; Fig. 3).

Time-course profiles of percentage changes in morning and evening PEF values are shown in Fig. 4. The percentage changes in both morning and evening PEF values significantly increased from 1 week after the start of study treatment ($P < 0.001$), and the improvement in PEF was maintained throughout the treatment period. A between-group comparison of percentage changes showed that the increases in morning PEF ($P < 0.05$ at weeks 1, 2, 3, and 4) and evening PEF ($P < 0.05$ at weeks 1, 3, 4, 6, and 8; $P < 0.01$ at week 5) were significantly greater in the Tio + Tulo group than in the Tio group.

Severity of dyspnea was evaluated using the Medical Research Council dyspnea scale at the start and end of study treatment ($P < 0.001$ for each). Although dyspnea decreased significantly in both treatment groups, the differences were very similar (Table 2).

Regarding QOL, the mean baseline QOL score was higher in the Tio + Tulo group than the Tio group. The total SGRQ score decreased significantly from baseline in the Tio + Tulo group only ($P < 0.001$). The change was an improvement of more than four points, which is defined as the minimal clinically important difference value. An improvement of four or more points was also observed in each component (symptoms, activity, and impact) of the SGRQ, with significant differences in activity ($P < 0.05$) and impact ($P < 0.001$). In a between-group comparison of changes, improvements in the impact and total scores of the SGRQ were significantly greater in the Tio + Tulo group than in the Tio group ($P < 0.05$ for each) (Fig. 5).

Safety

The following adverse events suspected to be related to study treatment were observed in the Tio group: urticaria (mild) in one subject, reduced masticatory force (mild) in one subject, and dysuria (moderate) with increased blood pressure (moderate) in one subject. Headache (mild) was observed in one subject in the Tio + Tulo group (Table 3).

Discussion

We conducted a study in which a β_2-agonist, tulobuterol, in a patch preparation, was given in combination with inhaled tiotropium (an anticholinergic) to stable COPD patients for 8 weeks. As a result of this treatment, FVC and FEV_1 improved significantly from baseline, but the changes were not significantly different from those observed in the Tio group. On the other hand, a significant improvement in IC from baseline was observed in the Tio + Tulo group, but not in the Tio group. A between-group comparison of percentage changes in IC revealed a significant improvement in the Tio + Tulo group. In addition, the percentage changes in the morning and evening PEF values improved significantly in the Tio + Tulo group compared with the Tio group. The change in total SGRQ score as a measure of QOL was significantly greater in the Tio + Tulo group than in the

Table 1 Patient characteristics (mean or mean ± SD).

	Treatment group	
	Tio group	Tulo + Tio group
Patients (n)	39	44
Males (%)	94.9	97.7
Age (years)	69.9 ± 5.5	70.2 ± 7.4
Height (cm)	163.14 ± 7.36	164.46 ± 5.63
Weight (kg)	58.29 ± 7.8	59.84 ± 9.79
Severity by GOLD stage (%)		
II	64.1	41.9
III	35.9	58.1
Current smokers (%)	23.1	31.8
Concomitant medication (%)		
Theophyllines	25.6	36.4
Expectorants	17.9	20.5
Short-acting β_2 agonists	10.3	15.9
Dyspnea (MRC scale)	2.5 ± 0.8	2.6 ± 0.9
Pulmonary function tests[a]		
FVC (L)	2.93 ± 0.66	2.92 ± 0.69
FEV_1 (L)	1.39 ± 0.41	1.20 ± 0.35
FEV_1% (%)	47.6 ± 10.8	42.2 ± 9.50
%FEV_1 (%)	53.7 ± 14.7	45.8 ± 12.8
IC (L)	2.01 ± 0.44	1.94 ± 0.47
PEF[a] (L/min)		
Morning	237.3 ± 80.4	218.4 ± 79.0
Evening	246.2 ± 78.3	225.4 ± 81.5
Quality of life scores[a] (units)		
Symptoms	43.1 ± 19.1	51.8 ± 20.1
Activity	45.0 ± 22.2	49.5 ± 19.9
Impact	19.5 ± 12.3	26.6 ± 14.7
Total SGRQ	31.9 ± 14.3	38.7 ± 13.6

GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council; PEF, peak expiratory flow; SGRQ, St. George's Respiratory Questionnaire.
[a] Before the run-in period (during treatment with bronchodilators).

Tio group, as was the change in impact score, a component of the SGRQ.

According to the GOLD, the international initiative establishing guidelines for treatment of COPD, drug therapy with bronchodilators is regarded as the mainstream treatment. Bronchodilators include long-acting agents such as anticholinergics, β_2-agonists and methylxanthines. These agents have different mechanisms of action, and are used according to the responsiveness and symptoms of individual patients. When symptoms are not well controlled, the combined use of bronchodilators with different mechanisms of action is recommended in view of the main and adverse effects, rather than increasing the dose of a single agent.[1] According to the reports of van Noord and colleagues,[10,15] combination therapy with inhaled tiotropium and inhaled formoterol improves pulmonary function better than monotherapy with each agent, and also improves airflow obstruction, resting hyperinflation, and the frequency of rescue therapy with short-acting β_2-agonists, compared with monotherapy with inhaled tiotropium. We selected anticholinergics because the reversible airway contraction in COPD patients mainly depends on acetylcholine released from the vagal nerve, and realized the clinical usefulness of the combined use of an anticholinergic with a β_2-agonist, which stimulates β_2-receptors in airway smooth muscle. The GOLD recommends the use of an inhaled formulation of bronchodilators for COPD treatment, from the standpoint of efficacy and safety. However, because many COPD patients are elderly, their adherence to inhalation therapy becomes an issue. Therefore, as an option to enhance the treatment effect, a dosage form that allows better patient adherence can be selected if acceptable in terms of safety. Although long-acting anticholinergics for COPD treatment are available only in inhaled formulations, long-term β_2-agonists are available in patch formulations as well as in inhaled formulations.

Transdermal tulobuterol is a β_2-agonist designed to maintain drug levels at constant effective concentrations over a 24-h period when applied once daily. In addition, it has an improved safety profile, with a lower maximum blood drug concentration.[12,13] Tamura and coworkers reported that treatment adherence is better with the patch formulation than with the inhaled formulation.[16] Among long-acting β_2-agonists, inhaled salmeterol in a twice-daily regimen is globally used.[17,18] Recently, we conducted a randomized parallel-group comparison study using inhaled salmeterol and transdermal tulobuterol. The study showed that transdermal tulobuterol, compared with inhaled salmeterol, has an equivalent effect in improving pulmonary function, such as FEV_1, FVC, and morning and evening PEF values, and is significantly superior in

Table 2 Changes in pulmonary function, severity of dyspnea, and quality of life scores (mean ± SD).

Parameter	Tio group			Tio + Tulo group			Comparison between-groups
	Baseline	Week 8	Change	Baseline	Week 8	Change	
FVC (L)	2.94 ± 0.11	3.16 ± 0.11***	0.22 ± 0.05	2.91 ± 0.11	3.18 ± 0.10***	0.28 ± 0.05	$P = 0.5379$
FEV_1 (L)	1.38 ± 0.07	1.52 ± 0.07***	0.14 ± 0.03	1.24 ± 0.06	1.37 ± 0.07***	0.13 ± 0.03	$P = 0.6813$
%FEV_1 (%)	50.5 ± 1.97	55.7 ± 1.84***	5.26 ± 0.91	44.3 ± 1.70	49.1 ± 1.89***	4.80 ± 0.93	$P = 0.6948$
IC (L)	2.02 ± 0.07	2.09 ± 0.08	0.07 ± 0.05	1.96 ± 0.08	2.10 ± 0.07*	0.14 ± 0.06	$P = 0.2837$
Dyspnea (MRC scale)	2.5 ± 0.8	2.1 ± 0.8***	−0.3 ± 0.5	2.6 ± 0.9	2.1 ± 0.8***	−0.5 ± 0.6	$P = 0.3798$
Total SGRQ (units)	31.6 ± 2.36	29.6 ± 2.52	−1.96 ± 1.16	38.4 ± 2.04	32.0 ± 2.22***	−6.48 ± 1.72	$P = 0.0325$

MRC, Medical Research Council; SGRQ, St. George's Respiratory Questionnaire.
*$P < 0.05$, ***$P < 0.001$ (within-group comparison: paired t-test).
Comparison between-groups: Wilcoxon rank sum test.

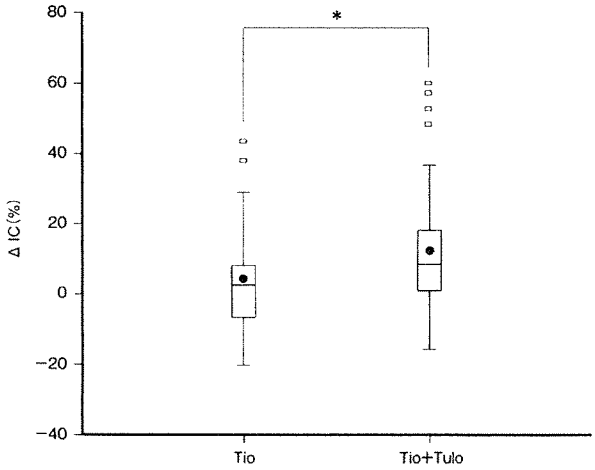

Figure 3 Effect of tulobuterol used in combination therapy on percentage change in IC. The percentage change from baseline at week 8 was assessed in each group. Between-group comparisons were performed for percentage changes. $^{*}P < 0.05$ (Tio group versus Tio + Tulo group); between-group comparison using the Wilcoxon rank sum test DIF, difference.

improving sleep scores. In addition, only transdermal tulobuterol resulted in a significant improvement in QOL (total SGRQ score) from baseline.[14] These findings confirmed that transdermal tulobuterol can replace inhaled salmeterol. Therefore, the use of transdermal tulobuterol, selected as a long-acting β_2-agonist, in combination with inhaled tiotropium for long-term management of COPD, is considered a promising treatment option.

In the present study, in which transdermal tulobuterol was used in combination with inhaled tiotropium, only the Tio + Tulo group showed a significant improvement in IC from baseline, with a significant between-group difference in percentage change in IC. This may be because extensive bronchodilation involving peripheral airways was induced by the combined use of transdermal tulobuterol with inhaled tiotropium, and because the drug was delivered to a wider extent of the airway through the blood circulation.[19,20] In fact, the morning and evening PEF values were significantly increased in both groups, and the percentage change in either morning PEF or evening PEF tended to show more significant improvement in the Tio + Tulo group than in the Tio alone group. These findings suggest that the combined use of transdermal tulobuterol with inhaled tiotropium improves obstruction of the central and peripheral bronchi more than monotherapy with inhaled tiotropium. FEV_1 and PEF are both central airway parameters; theoretically, the FEV_1 should change in the same manner as the PEF. No significant difference in FEV_1 was observed, and only the PEF showed a significant difference, probably because the FEV_1 change was small while, conversely, the change in PEF was large.

We propose the following possible explanations for the additive effects of transdermal tulobuterol and tiotropium. First, the effects of β_2-agonists and anticholinergic agents may be additive because β_2 receptors and muscarinic receptors (M_3) have different mechanisms of action. A recent report[10] described additive effects of β_2-agonists and anticholinergic agents. Second, β_2 receptors and muscarinic receptors (M_3) are both distributed in central and distal airways.[21] Theoretically both agents affect all airways. However, vagal nerve fibers mainly innervate central airways.[22] Therefore stimulated muscarinic receptors (M_3) may be mainly found in central airways. Anticholinergic agents may improve function in central airways rather than peripheral airways because they block cholinergic impulses derived from vagal nerve fibers. Of course, it is also possible that peripheral muscarinic receptors (M_3) are stimulated by acetylcholine of non-neuronal origin.

Regarding the treatment of COPD, it has been reported that improvements not only in pulmonary function but also in QOL are important.[23–26] The results of the present study, in which transdermal tulobuterol was used in combination with inhaled tiotropium, showed significant improvements in the total SGRQ score as well as its activity and impact scores in the Tio + Tulo group compared with the Tio group. The SGRQ is a disease-specific health-related QOL index in COPD patients. The SGRQ consists of 'symptoms', assessing distress owing to respiratory symptoms; 'activity', assessing the effects of disturbance of mobility and physical activity caused by dyspnea; and 'impact', assessing the psychologic and social impact of the disease on daily life and well-being.[27,28] Of the three components, the impact score is highly important as a measurement of health-related

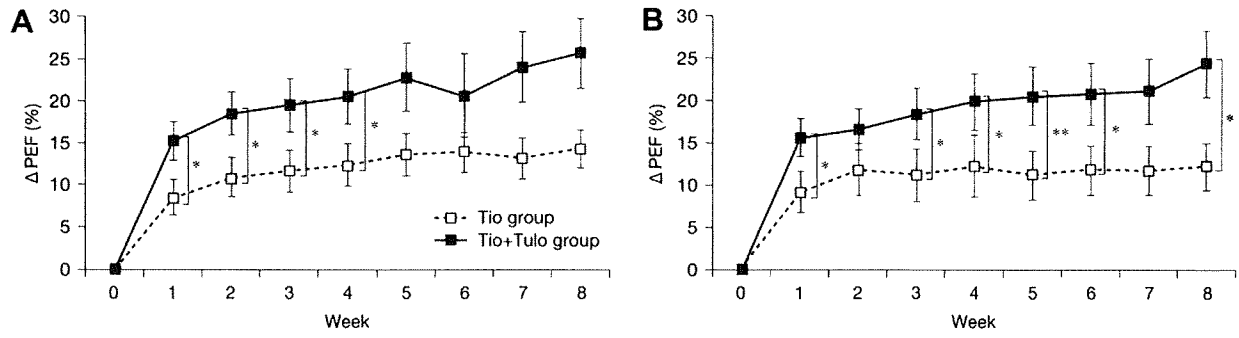

Figure 4 Effect of tulobuterol used in combination therapy on (A) morning and (B) evening peak expiratory flow (PEF). Between-group comparisons were performed for percentage changes. Within-group comparison: Wilcoxon signed rank test, $P < 0.001$ (versus baseline) for all measurements. Between-group comparison: Wilcoxon rank sum test; $^{*}P < 0.05$, $^{**}P < 0.01$ (Tio group versus Tio + Tulo group).

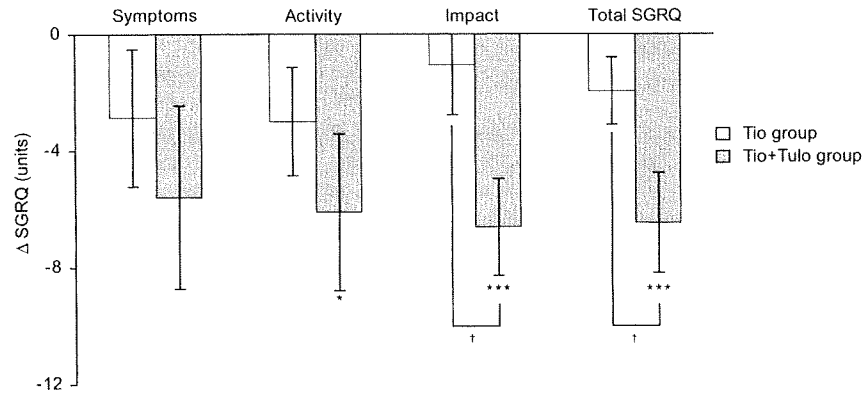

Figure 5 Effect of tulobuterol used in combination therapy on quality of life (St. George's Respiratory Questionnaire, SGRQ, scores). Between-group comparisons were performed to assess changes. Within-group comparison: paired *t*-test; $^{*}P < 0.05$, $^{***}P < 0.001$ (versus baseline). Between-group comparison: Welch's *t*-test, $\dagger P < 0.05$ (Tio group versus Tio + Tulo group).

QOL. Therefore, the improvement in the impact score induced by the combined use of transdermal tulobuterol is significant. The reason for the improvement of QOL by the combined use of transdermal tulobuterol may be that tulobuterol improved peripheral airway obstruction extensively via the systemic circulation, resulting in a reduction in pulmonary hyperinflation.[29,30] Regarding this point, de Torres and associates have reported that the effect of improving IC correlates with a change indicating an improvement in QOL.[31]

Regarding safety, adverse effects were observed in three subjects in the Tio group and one subject in the Tio + Tulo group, but none of these effects were serious. This result suggests that the combined use of transdermal tulobuterol with inhaled tiotropium does not increase the risk of adverse effects.

There are some limitations of the present study. First, because this study was an open-label study, it is possible that biases on the part of patients and/or investigators influenced patient-reported outcomes and other factors in the SGRQ. Second, the imbalance in the baseline QOL scores might have contributed to the difference in the change from baseline between the two groups, because the Tio + Tulo group had more room for improvement. Third, the cardiovascular effects of the two bronchodilators were not objectively assessed. It seems that tulobuterol affected the small airways following systemic delivery. This effect will have to be evaluated in a future study. However, the present findings demonstrate the additive effects of transdermal tulobuterol to inhaled tiotropium. The observed additive effect of transdermal tulobuterol is suggested to be due to a reduction in pulmonary hyperinflation resulting from the drug's effect in improving peripheral airflow obstruction via the systemic circulation. In COPD patients, many of whom are elderly, the combined use of inhaled tiotropium and transdermal tulobuterol is considered to be an ideal combination therapy for COPD.

Table 3 Safety (frequency of adverse events).

No.	Symptom	Tio	Tio + Tulo
1	Palpitation	0	0
2	Increased blood pressure (self-monitoring)	1	0
3	Finger tremor	0	0
4	Sputum	1	0
5	Urticaria	1	0
6	Reduced masticatory force	1	0
7	Dysuria	1	0
8	Pollakiuria	0	0
9	Headache	0	1

Conflict of interest statement

We have no conflicts of interest to declare.

Role of the funding source

The funding source had no role.

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References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management, and prevention of chronic obstructive pulmonary disease. Update 2008. Online. Available, <http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003>.
2. Littner MR, Ilowite JS, Tashkin DP, et al. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;**161**:1136–42.
3. van Noord JA, Bantje TA, Eland ME, Korducki L, Cornelissen PJ. Dutch Tiotropium Study Group. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax* 2000;**55**:289–94.
4. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;**19**:217–24.
5. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: A randomized trial. *Ann Intern Med* 2005;**143**:317–26.
6. Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. *Thorax* 2006;**61**:854–62.
7. Tashkin D, Kesten S. Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. *Chest* 2003;**123**:1441–9.
8. Casaburi R, Kukafka D, Cooper CB, Witek Jr TJ, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005;**127**:809–17.
9. Dusser D, Bravo ML, Iacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. *Eur Respir J* 2006;**27**:547–55.
10. van Noord JA, Aumann JL, Janssens E, et al. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest* 2006; **129**:509–17.
11. Tashkin DP, Celli B, Senn S, et al. UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;**359**:1543–54.
12. Uematsu T, Nakano M, Kosuge K, Kanamaru M, Nakashima M. The pharmacokinetics of the β_2-adrenoceptor agonist, tulobuterol, given transdermally and by inhalation. *Eur J Clin Pharmacol* 1993;**44**:361–4.
13. Iikura Y, Uchiyama H, Akimoto K, et al. Pharmacokinetics and pharmacodynamics of the tulobuterol patch, HN-078, in childhood asthma. *Ann Allergy Asthma Immunol* 1995;**74**: 147–51.
14. Fukuchi Y, Nagai A, Seyama K, et al. Research Group TB. Clinical efficacy and safety of transdermal tulobuterol in the treatment of stable COPD: an open-label comparison with inhaled salmeterol. *Treat Respir Med* 2005;**4**:447–55.
15. van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J* 2005; **26**:214–22.
16. Tamura G, Ohta K. Adherence to treatment by patients with asthma or COPD: comparison between inhaled drugs and transdermal patch. *Respir Med* 2007;**101**:1895–902.
17. Rennard SI, Anderson W, ZuWallack R, et al. Use of a long-acting inhaled β_2-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:1087–92.
18. Tashkin DP, Cooper CB. The role of long-acting bronchodilators in the management of stable COPD. *Chest* 2004;**125**:249–59.
19. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004;**364**:709–21.
20. Sturton G, Persson C, Barnes PJ. Small airways: an important but neglected target in the treatment of obstructive airway diseases. *Trends Pharmacol Sci* 2008;**29**:340–5.
21. Mak JCW, Barnes PJ. Autoradiographic visualization of muscarinic receptor subtypes in human and guinea pig lung. *Am Rev Respir Dis* 1990;**141**:1559–68.
22. Barnes PJ. Neural control of human airways in health and disease. *Am Rev Respir Dis* 1986;**134**:1289–314.
23. Niewoehner DE. The impact of severe exacerbations on quality of life and the clinical course of chronic obstructive pulmonary disease. *Am J Med* 2006;**119**(10 Suppl. 1):38–45.
24. Fan VS, Curtis JR, Tu SP, McDonell MB, Fihn SD. Ambulatory Care Quality Improvement Project Investigators. Using quality of life to predict hospitalization and mortality in patients with obstructive lung diseases. *Chest* 2002;**122**:429–36.
25. Yohannes AM, Roomi J, Waters K, Connolly MJ. Quality of life in elderly patients with COPD: measurement and predictive factors. *Respir Med* 1998;**92**:1231–6.
26. Gross NJ. Chronic obstructive pulmonary disease outcome measurements: what's important? what's useful? *Proc Am Thorac Soc* 2005;**2**:267–71.
27. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med* 1991;**85**(Suppl. B):25–31.
28. Jones PW. Quality of life measurement for patients with diseases of the airways. *Thorax* 1991;**46**:676–82.
29. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**:542–9.
30. van Noord JA, de Munck DR, Bantje TA, Hop WC, Akveld ML, Bommer AM. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. *Eur Respir J* 2000;**15**:878–85.
31. de Torres JP, Casanova C, Hernández C, et al. Gender associated differences in determinants of quality of life in patients with COPD: a case series study. *Health Qual Life Outcomes* 2006;**4**:72.