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Formoterol mono- and combination therapy with tiotropium in patients with COPD: A 6-month study

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Summary
Although guidelines recommend combining long-acting bronchodilators in COPD, data are limited. We examined the clinical efficacy and safety of formoterol, tiotropium and the combination in patients with COPD.

Eight hundred and forty-seven patients with COPD (mean FEV_1 52% predicted; FEV_1/FVC 53%) were randomized to receive one of the following four treatments for 24 weeks: formoterol 10 μg b.i.d. plus tiotropium 18 μg o.d.; formoterol 10 μg b.i.d.; tiotropium 18 μg o.d., or placebo. The study was partially blinded (formoterol and placebo).

For the primary endpoint, FEV_1 2 h post-dose after 24 weeks, there were small differences in favour of the combination therapy versus formoterol (0.07 L, $p = 0.044$) or tiotropium (0.06 L, $p = 0.066$). All three treatments were superior to placebo ($p < 0.001$). The combination was statistically superior to monotherapy for: the primary endpoint ($p = 0.044$ vs. formoterol); FEV_1 5 min after the first dose ($p < 0.001$) and at 12 weeks ($p < 0.05$ vs. tiotropium); and peak expiratory flow averaged over the first 6 weeks ($p < 0.001$ vs. both). The three active treatments were significantly more effective than placebo for secondary endpoints: COPD-related 'bad days', symptoms, use of rescue medication and peak expiratory flow, and aspects of health-related

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quality of life. The overall incidence of adverse events was similar with all active treatments, although COPD-related adverse events were more common with tiotropium.

Combined bronchodilator therapy may be a valuable treatment option for patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality world-wide, with a prevalence of more than 10% in the general population above the age of 40 years.[1] Bronchodilators are the mainstay of the management of COPD. Current management guidelines[2] recommend that patients with moderate or more severe COPD should receive treatment with one or more long-acting bronchodilators with different modes of action, with the expectation that patients will benefit from increased efficacy.

Formoterol (β_2-agonist) and tiotropium (anticholinergic) are long-acting bronchodilators with different mechanisms of action. In addition to their bronchodilator effect, both have been shown to improve health status and reduce exacerbations in COPD patients.[3–5] Formoterol has a fast onset and a bronchodilator effect of approximately 12 h[4], while tiotropium has a 24-h bronchodilator effect and is given once daily.[6]

The therapeutic potential of combining these two bronchodilators in patients with COPD was first demonstrated by Cazzola et al., both in stable disease[7,8] and in patients with acute exacerbations.[9] Short-term studies showed that combined therapy can improve airflow obstruction and resting hyperinflation.[10,11] More recently, 6-week studies have reported improved bronchodilation with the combination versus salmeterol plus fluticasone,[12] and improved bronchodilation, dyspnoea and rescue salbutamol use versus tiotropium alone.[13]

We set out to evaluate the efficacy of formoterol monotherapy and to determine whether the combination of formoterol twice daily with once-daily tiotropium would confer benefits for a range of efficacy variables over a 24-week treatment period. We were also interested to examine the safety profiles of these approaches to treatment.

Methods

Patients (inclusion/exclusion criteria)

The first patient was recruited in October 2004 and all patients completed the study by November 2005.

The study included males and females with stable COPD[14] aged $\geq$40 years at COPD onset and with a smoking history of $\geq$10 pack-years, forced expiratory volume in 1 second (FEV_1) $<$ 70% of patient's predicted normal value (and $\geq$1.00 L), and FEV_1/forced vital capacity (FVC) $<$ 70%. They were to be symptomatic on at least 4 of 7 days prior to randomization (symptom score $>$0 on diary card). The study excluded patients who had a respiratory tract infection or had been hospitalized for an acute exacerbation of COPD within the month prior to screening. Patients with a clinically significant condition such as ischaemic heart disease that might compromise patient safety or compliance were also excluded.

The study was conducted in outpatient and specialist clinics at 86 centres in Germany (30), Italy (19), Netherlands (9), Russian federation (9), Poland (7), Czech Republic (4), Spain (4) and Hungary (4).

Study design

A screening period of up to 4 weeks included 2 weeks for washout of disallowed medications and 2 weeks for eligibility assessment and baseline evaluations. Patients entered a 24-week treatment period and were randomized to one of four treatments: (1) formoterol 10 μg twice daily (b.i.d.) via multi-dose dry powder inhaler (MDDPI); (2) placebo b.i.d. via MDDPI; (3) tiotropium 18 μg once daily (o.d.) via the HandiHaler® + formoterol 10 μg b.i.d. via MDDPI, and (4) tiotropium 18 μg o.d. (in the morning) via the HandiHaler® + placebo b.i.d. via MDDPI. The dose of formoterol in the MDDPI has previously been shown to be similarly effective to the standard therapeutic dose of 12 μg administered via the single-dose device, the Aerolizer (Novartis).[15] The study was double-blind for treatment comparisons (1) vs. (2) and (3) vs. (4) (MDDPI only), but not for other comparisons as tiotropium was administered open-label. Randomization was not stratified.

Salbutamol pMDI (2×100 μg/puff) was permitted as rescue medication. Patients were asked not to use salbutamol in the 8 h before a study visit. Patients could receive inhaled corticosteroids (ICS) at a stable daily dose (any patients receiving fixed combinations of ICS and β_2-agonists were switched to receive the same dose of ICS and on-demand salbutamol).

Patients were instructed how to use the two inhaler devices containing study medication and were observed at each treatment visit to ensure correct inhalation technique, and re-trained if necessary. Patients were also instructed on the correct use of their existing, concomitant COPD medications.

Study assessments

Patients visited the clinic for efficacy and safety assessments at baseline and at 6-week intervals until completion. Spirometric assessments included FEV_1 and FVC measured at 5 min, 2 h and 3 h post-dose (the highest of three acceptable manoeuvres were recorded for each time point). Where possible, the same person evaluated a given patient throughout the study. Spirometers were always calibrated before measurements at each visit, and calibration reports were stored.

Disease-specific quality of life (QoL) was assessed by the St George's Respiratory Questionnaire (SGRQ).[16] Exercise

testing was by means of the 6-minute walking test, carried out 3 h post-dose at the end of treatment. The walk test was performed under standardized conditions,[17] in a level indoor corridor at least 33 m long with a 30 m distance marked off, unimpeded by other corridor traffic, and under trained supervision. Patients were asked to 'walk as far as you can in 6 minutes'.

Safety assessments included haematology and blood chemistry, and patients were assessed regularly for vital signs, electrocardiogram (ECG) and physical condition. All adverse events (AEs) were recorded. Patients also completed a daily diary card recording symptoms, peak expiratory flow (PEF) and rescue salbutamol use.

Study endpoints

The primary efficacy outcome was FEV_1 measured 2 h post-dose after 24 weeks of treatment. Secondary efficacy outcomes included: FEV_1 and FVC at other time points during the study (5 min, 2 and 3 h post-dose following the first dose of treatment, and after 12 and 24 weeks of treatment); COPD exacerbations; symptom scores, rescue medication use and PEF; quality of life, and 6-minute walking distance. According to the COPD exacerbations four different variables were defined: (1) 'bad days' were days with at least two symptoms recorded with a score of 2 or more (breathlessness, cough, wheeze, amount of sputum and colour of sputum were each recorded on a 0–3 scale); (2) 'COPD exacerbation days' were days where two or more of the same symptoms as above were recorded as being worse than usual; (3) 'COPD exacerbations requiring additional therapy' were COPD-related AEs requiring additional therapy, where COPD-related AEs were defined as AEs coding to the preferred terms: COPD, COPD exacerbated, cough, any term containing 'dyspnoea', lower respiratory tract infection, chronic bronchitis, bronchospasm, bronchial obstruction and respiratory failure; and additional therapy was any COPD therapy reported as being used to treat a COPD exacerbation, other than rescue bronchodilator; and (4) 'COPD-related hospitalizations'. A treatment plan was provided for acute COPD exacerbations detailing a regimen of oral corticosteroids and/or antibiotics; however, the treatment of exacerbations was ultimately at the investigators' discretion. Total daily symptom score and rescue use were recorded on daily diary cards, along with pre-medication morning PEF for the first 6 weeks of treatment. The SGRQ was administered at baseline and following 12 and 24 weeks of treatment. Six-minute walking distance was assessed at baseline and following 24 weeks of treatment. All endpoints were pre-specified.

Statistical analysis

Two previous studies of formoterol in COPD patients[4,18] were used to obtain an estimate of the between-patient standard deviation of 0.30 L in FEV_1 at 2 h post-dosing. To give 80% power to detect a clinically relevant difference of 0.12 L between formoterol and placebo[19] as being statistically significant at the 5% level using a two-sided test, approximately 100 patients per group were required. A separate objective was to collect safety data for patients aged 65 years and above, who (it was expected) would make up about half the population patients.[4,18] On this basis a sample size of approximately 200 patients per group was chosen to provide adequate power to test the primary objective and reasonable power to test the secondary objectives, while providing sufficient safety data in elderly patients.

FEV_1 and FVC were analysed using an analysis of covariance (ANCOVA) model including country, gender, reversibility ($<$15% or $\geq$15%), baseline smoking status (current or ex-smoker) and treatment as factors and baseline FEV_1 as covariate. PEF averaged over the first 6 weeks of treatment was analysed using a similar ANCOVA model, with mean PEF from the last 7 days of the screening period as the baseline value. The percentages of COPD bad days and exacerbation days were analysed using a similar ANCOVA model with the baseline value being the average over the 7 days prior to randomization. The number of patients with COPD exacerbations requiring additional therapy and those necessitating hospitalization were analysed using the Cochran–Mantel–Haenszel test stratified by country. Mean daily total symptom score (sum of scores for the five symptoms) and mean rescue use were analysed by the van Elteren test stratified by the baseline score. For QoL, the scores for three domains (symptoms, activity, impacts) and the total score were calculated and analysed using an ANCOVA model similar to that used for the primary variable. The 6-minute walking test was analysed using a similar model.

The intent-to-treat (ITT) population consisted of all randomized patients who received at least one dose of study medication. This population was used for efficacy and safety analyses. All analyses were performed at the 5% significance level (2-sided). Probability values were not adjusted for multiple comparisons.

Results

Patients

Of 1081 patients screened, 847 were randomized. The number of patients randomized per centre averaged 10 (range 1–32). The most common reasons that patients failed screening were unacceptable medical history or inappropriate spirometry evaluations, lung function being inappropriate (FEV_1 or $FEV_1/FVC > 70\%$ of predicted or $FEV_1 < 1.0$ L) to qualify for study entry. The disposition of patients and reasons for discontinuation are shown in Table 1. Some patients encountered difficulties using the MDDPI (used by all groups for delivering formoterol or placebo) and 20% specifically reported a device-related issue. Overall, 12–13% of patients discontinued early from the active treatments, compared with 14.4% of placebo patients. Details of the patients are shown in Table 2. All but two patients were Caucasian.

During the treatment period, between 40.6% and 43.9% of patients in each treatment group received treatment with budesonide, fluticasone or beclometasone.

Bronchodilator effect

For the primary variable, FEV_1 2 h post-dose after 24 weeks, there were numerical differences in favour of

Table 1 Patient disposition (*n*, %)

	Formoterol	Tiotropium	Tiotropium + formoterol	Placebo	Total
Screened					1081
Randomized	210 (100.0)	221 (100.0)	207 (100.0)	209 (100.0)	847 (100.0)
Completed	185 (88.1)	192 (86.9)	182 (87.9)	179 (85.6)	738 (87.1)
Patients discontinuing	25 (11.9)	29 (13.1)	25 (12.1)	30 (14.4)	109 (12.9)
Reason for discontinuing					
Subject withdrew consent	12 (5.7)	11 (5.0)	11 (5.3)	11 (5.3)	45 (5.3)
Adverse event(s)	6 (2.9)	13 (5.9)	8 (3.9)	8 (3.8)	35 (4.1)
Protocol violation	4 (1.9)	3 (1.4)	3 (1.4)	6 (2.9)	16 (1.9)
Lost to follow-up	2 (1.0)	0	0	0	2 (0.2)
Administrative problems	1 (0.5)	0	3 (1.4)	1 (0.5)	5 (0.6)
Unsatisfactory therapeutic effect	0	2 (0.9)	0	3 (1.4)	5 (0.6)
Death	0	0	0	1 (0.5)	1 (0.1)

combination over monotherapy, with estimated mean (95% CI) differences versus formoterol of 0.07 (0.00—0.14) L ($p = 0.044$) and versus tiotropium of 0.06 (−0.00—0.13) L ($p = 0.066$). All three active treatments were significantly more effective than placebo ($p < 0.001$), with estimated mean differences in excess of the threshold for clinical relevance of 0.12 L.[19] FEV_1 measurements after the first dose and after 24 weeks are shown in Fig. 1. Results for FVC (Fig. 2) closely followed those for FEV_1.

COPD exacerbations

Combination therapy and monotherapy showed no clear difference in the percentage of COPD-related bad days or exacerbation days. Significantly fewer patients treated with combination therapy and formoterol experienced exacerbations requiring additional treatment compared with those receiving placebo (Table 3). Only a small number of patients had COPD exacerbations requiring hospitalization, with no significant between-group differences (Table 3).

Symptoms, use of rescue salbutamol and PEF

Average daily symptom scores and use of rescue medication over the course of the study were statistically significantly lower with combination and monotherapies versus placebo (Table 4). Mean morning PEF during the first 6 weeks of treatment was significantly greater with combination therapy versus either monotherapy, with mean (95% CI) differences of 11.0 (5.4—16.7) L/min vs. tiotropium and 10.6 (4.9—16.3) L/min vs. formoterol (both $p < 0.001$).

Disease-specific QoL

Differences between the three treatments relative to placebo in the scores for the total and individual domains of the SGRQ are shown in Fig. 3A. There were no significant differences between combined therapy and either monotherapy (Fig. 3B). The scores showed a number of statistically significant improvements with active treatments relative to placebo, concentrated in the symptoms

Table 2 Demographic and background characteristics of patients (ITT population)

	Formoterol ($n = 210$)	Tiotropium ($n = 221$)	Tiotropium + formoterol ($n = 207$)	Placebo ($n = 209$)
Age (yrs)				
Mean (SD)	61.8 (8.8)	63.4 (9.5)	62.6 (8.8)	62.5 (8.6)
Range	40—82	43—83	43—82	42—82
Sex, *n* (%), male	159 (75.7)	175 (79.2)	164 (79.2)	162 (77.5)
Smoking history, pack years				
Mean (SD)	35.4 (18.0)	38.6 (19.3)	37.9 (18.2)	40.1 (22.8)
Range	10—120	10—120	10—120	8—150
Time since COPD diagnosis (yrs)				
mean (SD)	7.0 (6.0)	6.9 (6.3)	7.2 (7.0)	6.7 (6.1)
Range	0—30	0—35	0—33	0—35
FEV_1, L: mean (SD)	1.52 (0.39)	1.50 (0.39)	1.48 (0.36)	1.50 (0.39)
FEV_1, % predicted: mean (SD)	51.6 (10.6)	51.6 (11.2)	50.4 (10.5)	51.1 (11.0)
FEV_1/FVC (%): mean (SD)	54.6 (10.2)	54.4 (9.6)	53.2 (9.9)	53.5 (10.0)
FEV_1 reversibility (%)[a]: mean (SD)	11.4 (12.9)	9.9 (11.4)	11.0 (10.4)	11.4 (14.1)
FEV_1 reversible by ≥15%: *n* (%)	60 (28.6)	58 (26.2)	62 (30.0)	60 (28.7)

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ITT, intention to treat.
[a] % change in FEV_1 (absolute values) 30 min after inhaling salbutamol 400 μg, measured at the screening visit.

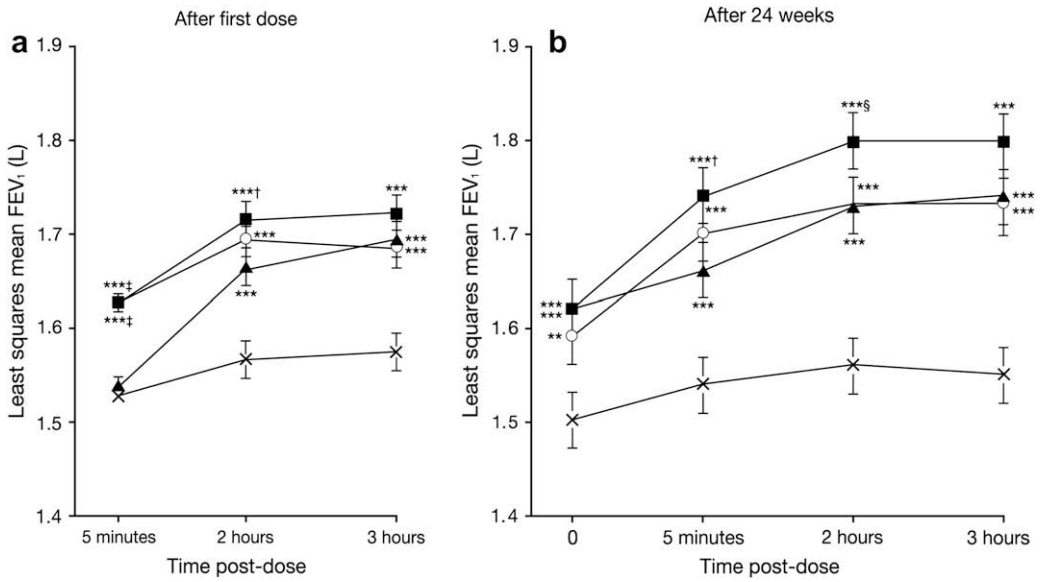

Figure 1 FEV_1 (±SE) measured after (a) the first dose of study treatment and (b) 24 weeks of treatment with formoterol (○), tiotropium (▲), tiotropium + formoterol (■) or placebo (×). ***$p < 0.001$, **$p < 0.01$ vs. placebo; ‡$p < 0.001$, †$p < 0.05$ vs. tiotropium, §$p < 0.05$ vs. formoterol.

component, which also reflected clinically relevant improvements that were most marked with combined treatment.

Walking distance

Estimated walking distances at the end of treatment, adjusting for baseline distance, were 434 m for combined treatment ($n = 179$), 417 m for placebo ($n = 180$), 425 m for formoterol ($n = 185$) and 428 m for tiotropium ($n = 189$). The difference between combined therapy and placebo was statistically significant ($p = 0.022$); however, the estimated difference of 17 m was below what is commonly accepted as the minimal clinically important difference, estimated to be 35–80 m.[20,21]

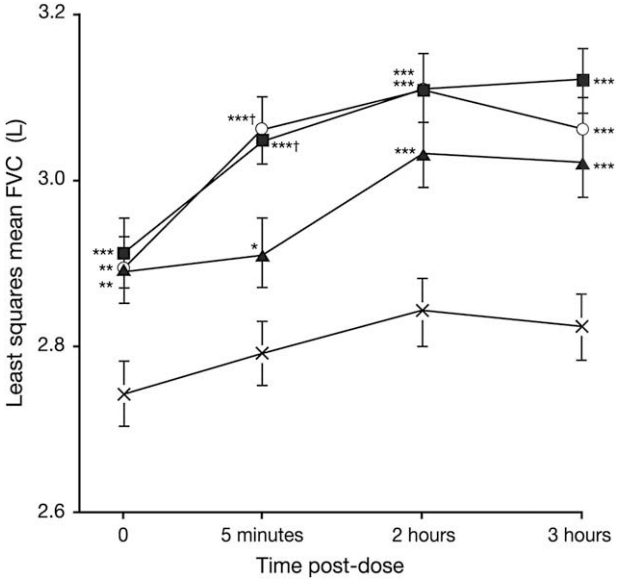

Figure 2 FVC (±SE) measured after 24 weeks of treatment with formoterol (○), tiotropium (▲), tiotropium + formoterol (■) or placebo (×). ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ vs. placebo; †$p < 0.05$ vs. tiotropium.

Safety

The overall incidence of adverse events was similar between placebo and the other treatment groups. Combined therapy did not appear to confer any increased risk compared with individual therapies, either in the whole population or the subgroup of patients aged ≥65 years (Table 5). Similarly, there were no indications of safety concerns affecting particular organ systems, including cardiac disorders. Most adverse events (87–92% of events in the active treatment groups) were mild or moderate in severity.

One patient in the placebo group died during the study after a fall. Of the serious adverse events, reported by 8–10 patients in each active treatment group, three were thought to be related to treatment: two cases of COPD exacerbation (one tiotropium and one combined treatment) and one case of tremor with formoterol. The case of tremor was mild in severity but classed as serious because it followed accidental mis-use of the inhaler, resulting in overdosage. Thirty-three patients overall had adverse events that led to withdrawal from the study; these were fairly equally distributed, with a small excess of cases of worsening COPD in the tiotropium treatment group. We also collected data for 'all COPD-related events', including additional related events such as cough, dyspnoea and bronchospasm. COPD-related events were most common with placebo (38 subjects; 18.2%), followed by tiotropium (32 subjects; 14.5%), formoterol (24 subjects; 11.4%) and

Table 3 Percentage of COPD-related 'bad days' and 'exacerbation days' over 24 weeks of treatment (% of treatment days, means and 95% CI), and number (%) of patients with COPD exacerbations requiring additional therapy and hospitalization (ITT population)

	Formoterol	Tiotropium	Tiotropium + formoterol	Placebo
COPD-related 'bad days' and 'exacerbation days' (means and 95% CI)				
Number of subjects	204	209	196	203
COPD-related bad days, % of treatment days	24.9[a]	25.6[a]	26.3[b]	33.9
	20.8–29.0	21.5–29.7	22.2–30.5	29.8–38.1
COPD exacerbation days, % of treatment days	2.4[c]	3.3	3.3	4.7
	1.0–3.8	1.9–4.7	1.9–4.7	3.4–6.1
Patients with COPD exacerbations requiring additional therapy and hospitalization				
Number of subjects	210	221	207	209
COPD exacerbations requiring additional therapy, *n* (%)	17 (8.1)[d]	23 (10.4)	13 (6.3)[e]	30 (14.4)
COPD exacerbations requiring hospitalization, *n* (%)	1 (0.5)	5 (2.3)	3 (1.4)	3 (1.4)

CI: confidence intervals. ITT: intention to treat.
[a] $p \leq 0.001$ vs. placebo (ANCOVA).
[b] $p = 0.004$ vs. placebo (ANCOVA).
[c] $p = 0.007$ vs. placebo (ANCOVA).
[d] $p = 0.041$ vs. placebo (Cochran–Mantel–Haenszel test).
[e] $p = 0.006$ vs. placebo (Cochran–Mantel–Haenszel test).

combined treatment (23 subjects; 11.1%). Such events were serious or led to premature discontinuation from the study in 7 (3.3%) subjects taking placebo, 9 (4.1%) taking tiotropium, 4 (1.9%) taking combined treatment and 4 (1.9%) taking formoterol.

Laboratory values and vital signs showed no statistically significant or clinically relevant changes with treatment; only isolated individual abnormal values or changes were seen. Results for serum potassium showed no significant differences between treatments at the end of the study: compared with placebo, differences were 0.02, 0.00 and 0.07 mmol/L for the formoterol, tiotropium and combined treatments, respectively. There was an unexpected shift to above-normal plasma potassium levels in 4–5% of subjects receiving formoterol (with or without tiotropium). β_2-agonists are known to decrease plasma potassium via skeletal muscle cell potassium uptake;[22,23] however, owing to artefacts several individual readings were known to be unreliable, and mean values did not differ significantly.

ECG measurements showed no differences in QTc interval between groups in mean values; abnormal values

Table 4 Symptom scores and rescue medication use averaged over baseline (the second week of screening) and the 24-week treatment period (ITT population)

	No. of patients with post-treatment data	Averaged daily total symptom score, median (range)		Averaged daily number of puffs of rescue medication, median (range)	
		Baseline	Treatment	Baseline	Treatment
Formoterol	206	5.00 (0.00–13.00)	4.29[b] (0.00–12.04)	2.43 (0.00–8.86)	1.30[b] (0.00–9.96)
Tiotropium	212	5.00 (0.57–13.57)	4.50[b] (0.04–13.72)	1.71 (0.00–15.14)	0.67[a] (0.00–10.57)
Tiotropium + formoterol	201	5.43 (0.00–11.29)	4.84[c] (0.01–15.00)	2.14 (0.00–10.29)	0.57[a] (0.00–8.00)
Placebo	206	5.14 (0.43–12.43)	5.20 (0.00–11.61)	2.00 (0.00–9.29)	1.77 (0.00–10.71)

ITT: intention to treat. Total daily symptom score = sum of scores for breathlessness, cough, wheeze, amount and colour of sputum, each scored on a 0–3 scale where 0 = no symptoms.
[a] $p \leq 0.001$ vs. placebo (van Elteren test stratified by baseline value).
[b] $p < 0.01$ vs. placebo (van Elteren test stratified by baseline value).
[c] $p < 0.05$ vs. placebo (van Elteren test stratified by baseline value).

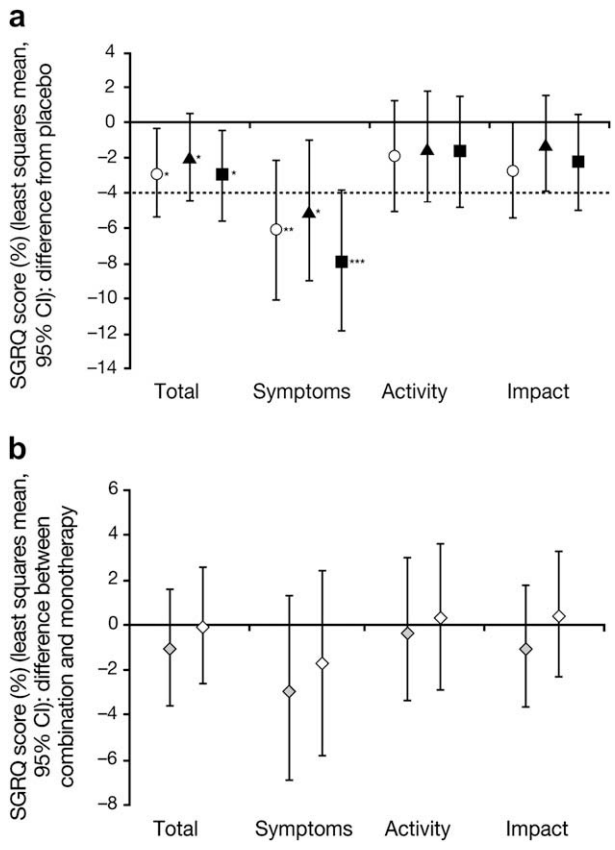

Figure 3 SGRQ scores (total and individual components) recorded after 24 weeks of treatment. (a) With formoterol (○), tiotropium (▲) or tiotropium + formoterol (■), including last (12-week) values for patients who did not complete the study: the graph shows differences between active and placebo treatment groups (ITT population). Negative values indicate improved quality of life relative to placebo. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ vs. placebo. Dashed line: minimum clinically important difference. (b) Differences between combined therapy versus tiotropium (◆) and versus formoterol (◇). Bars represent 95% CI.

or changes occurred with similar frequencies in the active treatment groups and were not more frequent with combination treatment.

Discussion

It is generally acknowledged that bronchodilators confer a range of benefits in patients with COPD, in whom the presence or absence of an acute bronchodilator response (reversibility) as assessed by FEV_1 does not predict long-term benefits such as symptom improvement and exercise tolerance, or even the future response to bronchodilators.[2,24–26] In this study, the benefits of long-acting bronchodilators in COPD were demonstrated in their efficacy relative to placebo in terms of bronchodilator effect (FEV_1 2 h post-dose, primary variable).

The combination of formoterol and tiotropium provided an improvement over either monotherapy. The size of this difference was less than has been previously observed in studies in patients with more severe COPD,[10,11,13] and in exacerbating COPD patients.[9] While it is possible that the bronchodilator effects of combined therapy may be greater in patients with more severe COPD, a 52-week study by Aaron et al., again in a more severe group of patients than in the present study, showed no additional effect on lung function (pre-bronchodilator FEV_1) with the addition of salmeterol to tiotropium, compared with tiotropium alone.[27] This is one of the first studies to study combination therapy in patients with relatively less severe COPD. Another recent study in patients with moderate COPD (50% were reversible) found superior bronchodilation with formoterol plus tiotropium compared with salmeterol plus fluticasone after 6 weeks, although other clinical outcomes were not explored.[12]

While the primary goal of the present study was to assess the bronchodilator effects and safety—especially in the elderly—of combined bronchodilator therapy, an additional aim was to define different characteristics of transient COPD deteriorations, or exacerbations. It is well known that the healthcare utilization-based definition of exacerbations can be misleading in a multinational study such as ours. Thus, we looked for four different categories for deterioration, defined variously as symptom-based and health care utilization-based. While the descriptions of exacerbations used in this study preceded the unified definition recently set down in the GOLD guidelines,[2] the definition of 'bad days' and 'exacerbation days' was not only a pre-specified endpoint in the study but was also sufficiently rigorously defined so as to be independent of national differences. Defining exacerbations in terms of healthcare utilization alone may otherwise undermine the reliability of the findings of multinational studies such as ours, conducted in countries with very different health care systems and accessibility.

Long-acting bronchodilator combination treatment showed similar effects irrespective of the symptom- and intervention-based definitions of exacerbations, respectively. Formoterol in particular had a significant effect on both COPD-related 'bad days' and 'exacerbation days', representing the milder end of the spectrum of exacerbations assessed in this study. Similar results have been reported elsewhere.[4,18] In one study,[28] mild exacerbations (days with high use of rescue medication) were reduced by a highly significant 55% with formoterol versus placebo in patients with moderate-to-severe COPD, while severe exacerbations were not affected.

The effectiveness of long-acting bronchodilators in controlling the symptoms of COPD is also reflected in the improvements in symptoms, use of rescue bronchodilator, PEF and quality of life (particularly the symptoms domain) in all treatment arms of the present study. We did not observe the same differential effects of combined therapy on symptoms and rescue use reported by Tashkin et al. in a more severe group of patients, although the combination arm demonstrated an 8-unit decrease in the symptoms domain.[13] It is possible that the advantages of combination therapy would be more apparent in more severe stages of COPD. In the study by Aaron et al.,[27] salmeterol plus tiotropium did not significantly reduce the proportion of patients with exacerbations (the primary endpoint) versus tiotropium monotherapy, although the incidence rate ratio for severe exacerbations requiring hospitalization was 0.83.

Table 5 Most frequent adverse events (affecting 2% or more of combination treatment group) (*n*, %) (ITT population) in (a) all patients and (b) patients aged ≥65 years

	Formoterol	Tiotropium	Tiotropium + formoterol	Placebo
(a) All patients	(*n* = 210)	(*n* = 221)	(*n* = 207)	(*n* = 209)
Any adverse event	72 (34.3)	79 (35.7)	70 (33.8)	82 (39.2)
COPD worsening	20 (9.5)	28 (12.7)	16 (7.7)	34 (16.3)
Nasopharyngitis	15 (7.1)	11 (5.0)	13 (6.3)	11 (5.3)
Cough	3 (1.4)	5 (2.3)	5 (2.4)	4 (1.9)
(b) Patients aged ≥65 years	(*n* = 83)	(*n* = 107)	(*n* = 93)	(*n* = 85)
Any adverse event	30 (36.1)	35 (32.7)	35 (37.6)	40 (47.1)
COPD worsening	11 (13.3)	11 (10.3)	9 (9.7)	17 (20.0)
Nasopharyngitis	5 (6.0)	5 (4.7)	5 (5.4)	2 (2.4)
Back pain	1 (1.2)	0	2 (2.2)	2 (2.4)
Cough	1 (1.2)	2 (1.9)	3 (3.2)	4 (4.7)
Hypertension	1 (1.2)	3 (2.8)	2 (2.2)	2 (2.4)
Shoulder pain	1 (1.2)	0	2 (2.2)	1 (1.2)
Oedema peripheral	0	0	3 (3.2)	0
Productive cough	0	0	2 (2.2)	0

ITT, intention to treat.

Although the latter reduction was not significant, the results raise the possibility that combination bronchodilator therapy may provide the most benefit, in terms of exacerbations, in patients with more advanced stages of disease. Further investigation in populations with clearly defined disease severity is required to clarify this possibility.

A potential limitation of this study arises from the only partially blinded nature of the study design, since a tiotropium placebo was not available and the formoterol versus tiotropium comparison therefore had to be open-label. Thus, patients knew if they were taking tiotropium, although not whether they were receiving formoterol or placebo from the MDDPI. Only the formoterol versus placebo and combination versus tiotropium comparisons were double blind, thus limiting the strength of the conclusions that can be drawn from other comparisons.

Another limitation could be that the 6 months' duration of the study did not allow exacerbations to be assessed reliably.[29] However, exacerbations were not the primary focus of the study; several long-term studies have assessed exacerbations reliably. Patients' continued use of inhaled corticosteroids may have attenuated any signal in respect of exacerbations. However, discontinuation prior to study inclusion prevents a reliable assessment of exacerbation frequency.[30]

In the present study, comparisons between combination and single therapies showed some statistically significant (although clinically small) differences in bronchodilator effect (FEV_1) and lung function (mean morning PEF). Significant differences were not apparent for exacerbations, QoL and walking distance. However, the combined approach tended to provide the most marked improvement relative to placebo for many variables, including walking distance and the symptoms component of quality of life. The study may have been underpowered to detect some of the differences between combination and monotherapy.

The combined bronchodilator approach did not appear to increase the burden of adverse events compared with individual treatments, either in the whole population or in the subgroup of older patients. This is an important consideration in a population of patients who are typically elderly and may suffer a range of co-morbidities that increase their vulnerability to, for example, adverse cardiac effects of treatment. It is reassuring that specific investigations of this effect with formoterol[31] or tiotropium[32] show little cause for undue concern.

The present study confirms the efficacy and safety of long-acting bronchodilators in patients with moderate COPD. The addition of formoterol to tiotropium treatment conferred small advantages in terms of the early bronchodilator effect, lung function measured at trough effect (PEF, pre-bronchodilator) or post-bronchodilator (FEV_1), and an indication of fewer exacerbations requiring additional treatment, although this was not statistically significant. The safety profile of the combination is comparable to either single therapy and may even be preferable in terms of fewer reports of COPD as an adverse event than with either single agent.

Conflict of interest statement

C.V. has given a variety of presentations at industry symposia sponsored by Altana, Astra Zeneca, Aventis, Bayer, Boehringer, Glaxo Smith Kline, Merck Darmstadt. He also received fees for consulting from Altana, Astra Zeneca, Bayer, Boehringer, Glaxo Smith Kline. P.K. has received speaker and consulting fees and reimbursement for attending conferences in Germany and abroad, he and his staff received fees for conducting clinical trials for following companies, potentially interested in the results of this study: AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Pfizer. S.H. has participated in an Academy project funded by Novartis Farma S.p.A., Italy. At the time of the study, S.S. was employed by Novartis. J.T. is an employee of Novartis.

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