

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD

V Brusasco, R Hodder, M Miravittles, L Korducki, L Towse, S Kesten

Thorax 2003;58:399-404

Background: A study was undertaken to record exacerbations and health resource use in patients with COPD during 6 months of treatment with tiotropium, salmeterol, or matching placebos.

Methods: Patients with COPD were enrolled in two 6-month randomised, placebo controlled, double blind, double dummy studies of tiotropium 18 µg once daily via HandiHaler or salmeterol 50 µg twice daily via a metered dose inhaler. The two trials were combined for analysis of health outcomes consisting of exacerbations, health resource use, dyspnoea (assessed by the transitional dyspnoea index, TDI), health related quality of life (assessed by St George's Respiratory Questionnaire, SGRQ), and spirometry.

Results: 1207 patients participated in the study (tiotropium 402, salmeterol 405, placebo 400). Compared with placebo, tiotropium but not salmeterol was associated with a significant delay in the time to onset of the first exacerbation. Fewer COPD exacerbations/patient year occurred in the tiotropium group (1.07) than in the placebo group (1.49, $p < 0.05$); the salmeterol group (1.23 events/year) did not differ from placebo. The tiotropium group had 0.10 hospital admissions per patient year for COPD exacerbations compared with 0.17 for salmeterol and 0.15 for placebo (not statistically different). For all causes (respiratory and non-respiratory) tiotropium, but not salmeterol, was associated with fewer hospital admissions while both groups had fewer days in hospital than the placebo group. The number of days during which patients were unable to perform their usual daily activities was lowest in the tiotropium group (tiotropium 8.3 (0.8), salmeterol 11.1 (0.8), placebo 10.9 (0.8), $p < 0.05$). SGRQ total score improved by 4.2 (0.7), 2.8 (0.7) and 1.5 (0.7) units during the 6 month trial for the tiotropium, salmeterol and placebo groups, respectively ($p < 0.01$ tiotropium v placebo). Compared with placebo, TDI focal score improved in both the tiotropium group (1.1 (0.3) units, $p < 0.001$) and the salmeterol group (0.7 (0.3) units, $p < 0.05$). Evaluation of morning pre-dose FEV₁, peak FEV₁ and mean FEV₁ (0-3 hours) showed that tiotropium was superior to salmeterol while both active drugs were more effective than placebo.

Conclusions: Exacerbations of COPD and health resource usage were positively affected by daily treatment with tiotropium. With the exception of the number of hospital days associated with all causes, salmeterol twice daily resulted in no significant changes compared with placebo. Tiotropium also improved health related quality of life, dyspnoea, and lung function in patients with COPD.

See end of article for authors' affiliations

Correspondence to:
Dr V Brusasco,
Dipartimento di Medicina
Interna, Università di
Genova, Viale Benedetto
XV 6, 16132 Genova,
Italy;
brusasco@dism.unige.it

Revised version received
15 January 2003
Accepted for publication
15 January 2003

Chronic obstructive pulmonary disease is an unremitting disease characterised by a decline in lung function over time and insidiously progressive impairment in health related quality of life (HRQoL). The most frequently reported symptom is dyspnoea on exertion.¹ Symptoms of the disease result in the need for medication and treatment from health-care providers. As the disease progresses, acute and subacute increases in symptoms (exacerbations) become more frequent and severe. Exacerbations may lead to hospital admissions and have a major influence on the use of health resources.²

Treatment with pharmacotherapy can improve symptoms and exercise tolerance.³ Treatment of exacerbations can provide more rapid recovery⁴ but preventing the onset of an exacerbation is preferable. Inhaled steroids have produced inconsistent results in terms of lung function and control of exacerbations.⁵⁻⁶ Inhaled bronchodilators such as anticholinergics and long acting inhaled β agonists provide symptomatic relief, possibly delay the onset of the first COPD exacerbation,⁷⁻⁸ and may decrease the long term incidence of exacerbations.⁸⁻¹⁰

Several anticholinergic formulations have been assessed in patients with COPD. Ipratropium, the most widely used, has a recommended dosing interval of four times daily. Oxitropium has only a slightly longer duration of action¹¹ and also requires

multiple daily dosing. Tiotropium is a novel anticholinergic agent with a much longer duration of action (>24 hours), presumably as a result of prolonged muscarinic receptor subtype (M_3) occupancy.¹²⁻¹³ Large long term clinical trials in patients with COPD have shown that once daily treatment with tiotropium affords more sustained bronchodilation and improvements in dyspnoea, HRQoL, and exacerbations than four times daily treatment with ipratropium.¹⁴⁻¹⁵ These observations suggest that tiotropium may reduce the use of health-care resources and improve the extent of disability from COPD.

Two 6-month studies were conducted to evaluate the efficacy of tiotropium in comparison with salmeterol and placebo in COPD. The two studies were identical except for the time of serial spirometric testing (12 hours v 3 hours). As stated a priori in the protocol, data from the two studies were combined to compare tiotropium and salmeterol with respect to various other health outcome end points including exacerbations and health resource use.

METHODS

Study design

Two 6-month studies were performed to compare tiotropium 18 µg once daily delivered by the HandiHaler and salmeterol

50 µg twice daily via a metered dose inhaler (MDI) in patients with COPD. The studies were performed in 18 countries and used a randomised, double blind, double dummy, parallel group design. There was no difference in the time of year of recruitment for the two trials.

Patients

Patients were required to have relatively stable airway obstruction with forced expiratory volume in 1 second (FEV₁) ≤65% of predicted normal and ≤70% of forced vital capacity (FVC), to be over 40 years of age, with a smoking history of >10 pack years. Patients with a history of asthma, allergic rhinitis, atopy, or with an increased total eosinophil count were excluded. Other exclusion criteria included use of supplemental oxygen or an upper respiratory tract infection in the 6 weeks before screening. Those patients with a significant disease other than COPD were not enrolled. A significant disease was defined as a disease that, in the opinion of the investigator, would put the patient at risk because of participation in the study or a disease which would influence the results of the study. The protocol was approved by independent ethics committees and informed consent was obtained from all patients.

Study protocol

A 2-week baseline period followed an initial screening visit. On completion of the baseline period, patients were entered into the 6-month randomised, double dummy period. At this time they received either tiotropium 18 µg once daily plus MDI placebo, salmeterol 50 µg twice daily plus HandiHaler placebo, or a combination of placebos.

Spirometric tests were conducted according to ATS guidelines¹⁶ before the start of treatment at 60 and 10 minutes before dosing at the randomisation visit and at 30, 60, 120 and 180 minutes after dosing. The tests were repeated at the same time intervals after 2, 8, 16 and 24 weeks of treatment. One of the two studies included spirometric tests being performed up to 12 hours following the morning dose during the aforementioned clinic days. The mean of the two FEV₁ (or FVC) values before the first dose of study medication was considered the baseline value while the mean of the two measurements just before dosing in the clinic at all other visits was considered as the trough value—that is, 23–24 hours after tiotropium or 11–12 hours after salmeterol.

Questionnaires assessing dyspnoea and HRQoL were administered at baseline and 8, 16 and 24 weeks following treatment. Dyspnoea was evaluated using the baseline dyspnoea index (BDI) and the transition dyspnoea index (TDI).¹⁷ The BDI and TDI consist of three axes (functional impairment, magnitude of task, and magnitude of effort) that are summed to create a focal score. The BDI was administered at the end of the baseline period and the TDI was administered at each of the follow up visits noted above. HRQoL was determined using the St George's Respiratory Questionnaire (SGRQ).¹⁸ The SGRQ is a disease specific instrument that contains 50 items in three subscales (symptoms, activity, and impact). Each response has an empirically derived weight. The total score is calculated from responses to all 50 items.

Detailed information on exacerbations of COPD, hospital admissions, concomitant medications, non-scheduled contacts with physicians and other healthcare providers, disability days, and employment status were collected. Information on exacerbations was reported as adverse events. Exacerbations were defined as a complex of respiratory symptoms (new onset or an increase in at least one of cough, sputum, dyspnoea, wheeze, chest discomfort) lasting at least 3 days and usually associated with a therapeutic intervention. Information on days hospitalised and use of the intensive care unit (ICU) was collected along with information on non-scheduled visits to the physician or other healthcare provider, disability days, and employment status.

Adverse events were assessed throughout the baseline and 24 week treatment periods. Laboratory testing, electrocardiograms, and physical examinations were conducted at baseline and at the final visit.

Data analysis

For the spirometry measurements, SGRQ total score, and TDI focal score, analysis of covariance was performed with the baseline being used as a covariate. In order to be able to include the same patients at each time point in the spirometry summaries, missing values were estimated using other values recorded for the patient on that test day. Linear interpolation between the two adjacent measurements was used to estimate random, middle, and missing spirometric measurements. For values at the end of the profiles that were missing because rescue medication was taken, the minimum observed FEV₁ value on that test day was used as the estimate. The last available value was used as the estimate for data that were missing for reasons unrelated to the patient's response to treatment. For the SGRQ, missing individual questions were imputed according to the guidelines established by the questionnaire developer. Data from missing SGRQ questionnaires were imputed using the last observation carried forward. Missing TDI questions were imputed using the last observation carried forward unless the patient discontinued due to worsening of COPD, in which case the least favourable observation was carried forward.

The percentage of patients with an improvement of at least 4 units (minimal clinically important difference) in SGRQ total score,¹⁸ an improvement in TDI focal score of at least 1 unit (minimally clinically important difference),¹⁷ adverse events, steroid bursts for COPD exacerbations, and with added theophylline for COPD exacerbations were analysed using Fisher's exact test. Each pair of treatments was examined separately.

The percentage of patients with at least one COPD exacerbation and the percentage with at least one hospital admission for a COPD exacerbation were analysed using logistic regression adjusted for the extent of exposure. Combining the two trials for evaluation of exacerbations was stated a priori in the trial protocols. The time to first COPD exacerbation and time to first hospital admission due to a COPD exacerbation were analysed using a log rank test. The number of exacerbations, number of exacerbation days, number of hospital admissions for an exacerbation, and number of days in hospital were analysed using the Wilcoxon-Mann-Whitney test. In all of these analyses each pair of treatments was considered separately.

For hospital admissions for any reason, unscheduled visits to a physician, and days unable to perform daily activities, missing data were estimated using multiple imputation with the Markov chain Monte Carlo method.¹⁹ In multiple imputation, rather than replacing each missing value with a single number, each is replaced with a set of numbers (for the present study, 10 imputations were done). The results of each imputation were analysed as complete data sets and the results of these analyses were combined. The number of hospital admissions and days in hospital due to all causes, the number of unscheduled visits and number of days unable to perform daily activities were analysed using analysis of variance with terms for treatment and centre. The percentage of patients with at least one hospital admission was analysed using the normal approximation to the binomial distribution. In all of the above a p value of <0.05 was considered statistically significant.

RESULTS

A total of 1207 patients participated in the studies; 402 were randomised to receive tiotropium, 405 to salmeterol, and 400 to placebo. Figure 1 shows a flow diagram of the number of

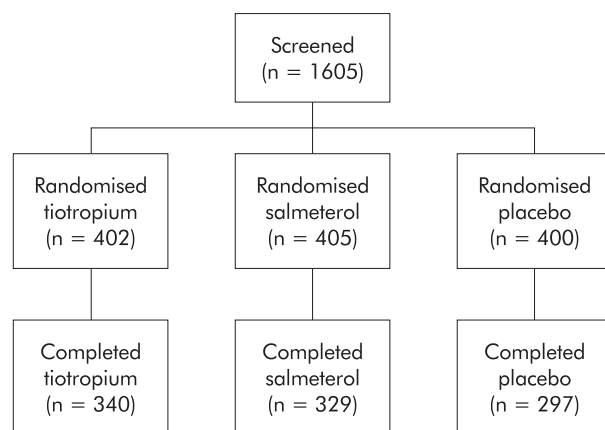


Figure 1 Flow diagram showing the number of patients screened, randomised, and completing the trial.

Table 1 Baseline demographic and lung function data of study patients. Data are expressed as mean (SD) unless otherwise noted.

	Tiotropium (n=402)	Salmeterol (n=405)	Placebo (n=400)
% Male	77.4	75.1	76.3
Age (years)	63.8 (8.0)	64.1 (8.5)	64.6 (8.6)
Duration of COPD (years)	9.0 (7.3)	9.9 (8.0)	9.8 (7.4)
Range	0.1–53	0.1–49	0.1–45
Smoking history (pack years)	44.1 (22.9)	44.8 (24.1)	42.4 (22.7)
FEV ₁ (l)	1.12 (0.39)	1.07 (0.38)	1.09 (0.40)
FEV ₁ /FVC (%)	43.7 (9.7)	42.2 (9.5)	42.3 (9.2)
FEV ₁ (% predicted)*	39.2 (11.6)	37.7 (11.7)	38.7 (12.1)
FVC (l)	2.59 (0.75)	2.55 (0.77)	2.60 (0.78)

FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity.

*Based upon ECCS.

patients screened, randomised, and completing the study for each treatment group. A significantly higher percentage of patients in the tiotropium group (84.6%) completed all visits than in the salmeterol (81.2%) and placebo (74.3%) groups ($p < 0.05$). This was principally due to a significantly smaller percentage of patients in the tiotropium group failing to complete because of adverse events (7.2%) compared with the salmeterol (14.8%) and placebo (16.0%) groups ($p < 0.01$).

Demographic data

The baseline demographic data of the patients were similar in all the groups (table 1). There were no differences in smoking history (mean for all patients 43.7 pack years). The mean screening FEV₁ was 1.12 l (39% of predicted) in the tiotropium group, 1.07 l (38% of predicted) in the salmeterol group, and 1.09 l (39% of predicted) in the placebo group.

Exacerbations

Tiotropium significantly delayed the time to the first COPD exacerbation compared with placebo ($p \leq 0.01$, fig 2). The proportion of patients with at least one exacerbation was 32%, 35% and 39% in the tiotropium, salmeterol, and placebo groups, respectively ($p > 0.05$). Patients treated with tiotropium had significantly fewer COPD exacerbations (and exacerbation days) per patient year than those treated with placebo ($p < 0.05$ for both, fig 3). The difference between salmeterol and placebo was not significant.

A total of 11.2% of patients in the tiotropium group used oral steroid bursts for the management of COPD exacerbations

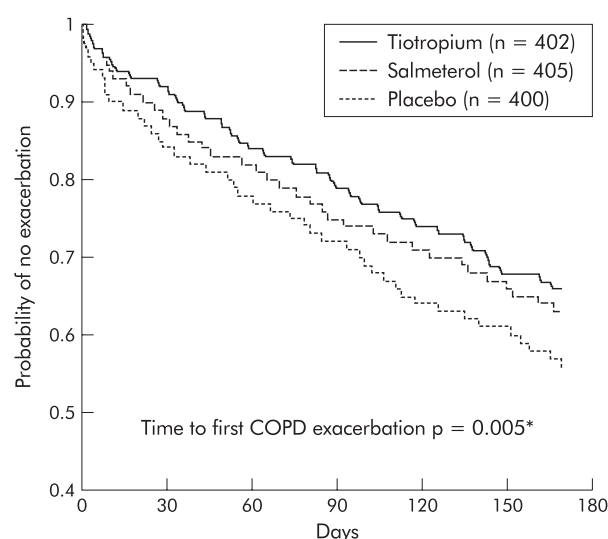


Figure 2 Kaplan-Meier estimates of the probability of no COPD exacerbations over 6 months of treatment. * $p = 0.005$ tiotropium versus placebo (log rank test).

compared with 13.8% of patients in the salmeterol group and 14.5% in the placebo group ($p > 0.05$ for all treatment comparisons). There was no statistically significant difference in the addition of or use of theophylline to treat exacerbations between treatment groups.

The time to first hospital admission for a COPD exacerbation did not differ between any two treatment groups. The percentages of patients with one or more hospital admissions associated with COPD exacerbations over the 6-month treatment period were 3%, 5%, and 5% for the tiotropium, salmeterol and placebo groups, respectively ($p > 0.05$ for all treatment comparisons). Patients treated with tiotropium had fewer hospital admissions related to COPD exacerbations than those treated with placebo or salmeterol. Patients treated with both tiotropium and salmeterol had fewer days in hospital for COPD exacerbations than the placebo group. However, the difference between the treatment groups for both the number of hospital admissions and the number of days in hospital was not statistically significant (table 2).

Health resource use and restricted activity

The number of hospital admissions and days in hospital for any cause was lower in both the tiotropium and salmeterol groups than in the placebo group; however, the difference for salmeterol was not statistically significant (table 2). A significantly lower proportion of patients required admission to hospital in the tiotropium group (12.0%) than in the placebo group (22.5%) but not the salmeterol group (16.0%). In addition, tiotropium was associated with fewer unscheduled physician visits for all causes. The lowest number of days on which patients were unable to perform their usual daily activities due to any cause was observed in the tiotropium group (8.3 (0.8) days) compared with 11.1 (0.8) days in the salmeterol group and 10.9 (0.8) days in the placebo group ($p < 0.05$).

HRQoL and dyspnoea

In the combined studies the SGRQ total score improved by 4.2 (0.7), 2.8 (0.7), and 1.5 (0.7) units during the 6 month trial for the tiotropium, salmeterol and placebo groups, respectively. A significant difference was observed for tiotropium *v* placebo ($p < 0.01$). The percentage of patients achieving an improvement of at least 4 units was 48.9%, 43.2%, and 39.3% for the tiotropium, salmeterol, and placebo groups, respectively ($p < 0.05$ for tiotropium *v* placebo). In both studies only tiotropium was associated with a statistically significant improvement in the proportion of patients achieving a change in the

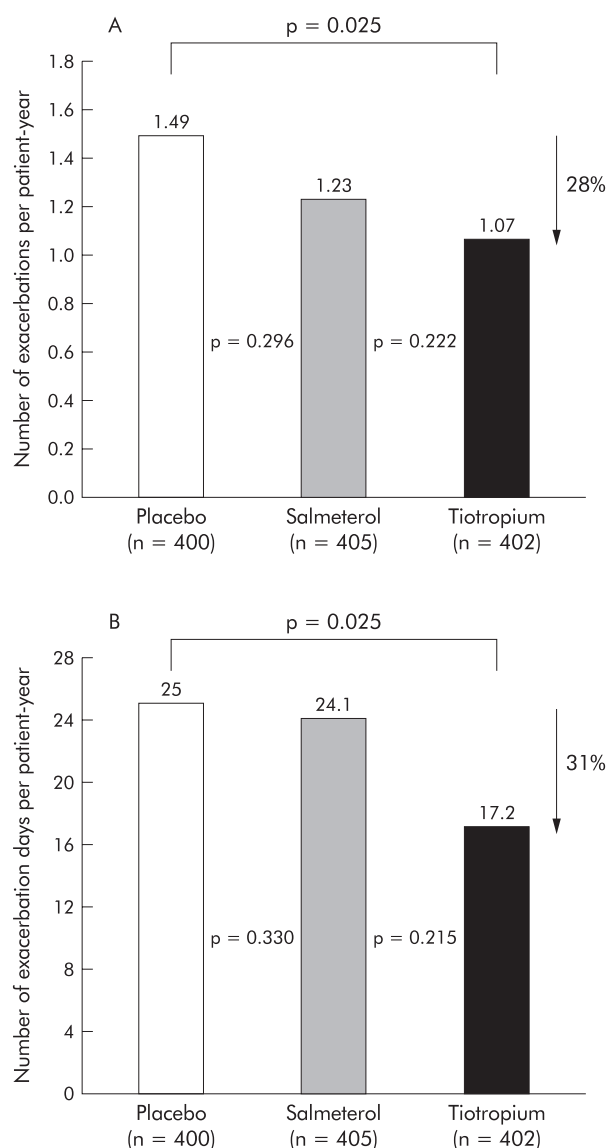


Figure 3 Number of (A) COPD exacerbations and (B) exacerbation days.

SGRQ total score of at least 4 units, while salmeterol was associated with this finding in one of the two studies.

In the combined study TDI focal score improved in both the tiotropium (1.1 (0.3) units) and salmeterol (0.7 (0.3) units) groups compared with placebo ($p < 0.001$ and $p < 0.05$, respec-

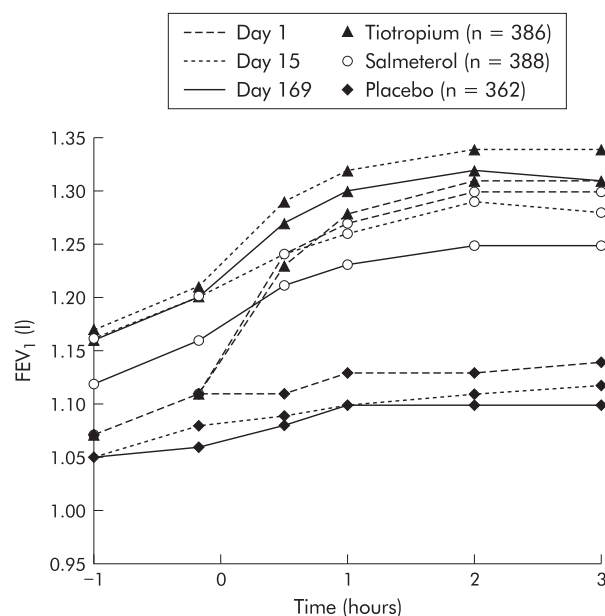


Figure 4 Mean FEV₁ before and after treatment on days 1, 15 and 169 of study; $p < 0.001$ for tiotropium versus placebo on all test days after treatment; $p < 0.05$ for tiotropium versus salmeterol on all test days except day 1 and -1 hour on day 15.

tively), without a significant difference between the tiotropium and salmeterol groups ($p = 0.17$). A higher percentage of patients achieved a change of at least 1 unit with the active drugs (tiotropium 43.1%, salmeterol 41.2%) than with placebo (29.8%, $p < 0.01$). In both studies only tiotropium was associated with a statistically significant improvement in the proportion of patients achieving a change in the TDI focal score of at least 1 unit, whereas salmeterol was associated with this finding in one of the two studies.

Spirometric tests

Following the first dose of study medication, both tiotropium and salmeterol showed equal efficacy compared with placebo in trough, peak and mean FEV₁. Following multiple dosing, tiotropium was more effective than salmeterol (fig 4). The mean improvement in trough FEV₁ for tiotropium and salmeterol was 0.12 (0.1) l and 0.09 (0.1) l, respectively ($p < 0.01$ for both) compared with placebo on the last day of the study, while trough FEV₁ in the tiotropium group was improved compared with salmeterol ($p < 0.05$). In the combined and individual studies tiotropium was statistically superior to salmeterol in peak FEV₁ and the area under the curve from 0 to 3 hours. For trough FEV₁ values tiotropium

Table 2 Mean (SE) health resource use and days of restricted activity during 6 months of treatment

	Tiotropium	Salmeterol	Placebo
Exacerbations†			
Hospital admissions	0.10	0.17	0.15
Days in hospital	0.98	1.14	1.88
Unscheduled physician visits	1.51 (0.22)	1.73 (0.22)	1.51 (0.22)
All cause†			
Hospital admissions	0.43* (0.22)	0.65 (0.00)	0.86 (0.22)
Days in hospital	2.38* (0.65)	3.46** (0.65)	4.97 (0.65)
Unscheduled physician visits	2.16 (0.22)	2.59 (0.22)	2.59 (0.22)
Days of restricted activity‡ (all cause)	8.3* (0.8)	11.1 (0.8)	10.9 (0.8)

* $p < 0.05$ tiotropium v placebo; ** $p < 0.05$ salmeterol v placebo.

†Expressed as events per patient year.

‡Expressed as events per 24 patient weeks

was statistically superior in the combined studies and one of the two studies.

Adverse events

Dryness of the mouth was the only event that was statistically higher with tiotropium (8.2%) than with salmeterol (1.7%) or placebo (2.3%). Mouth dryness led one patient to discontinue treatment with tiotropium. There was one death reported in the tiotropium group, six in the salmeterol group, and five in the placebo group. The one death in the tiotropium group was due to a ruptured abdominal aortic aneurysm. Two of the six deaths in the placebo group were due to cardiac arrest (one associated with a COPD exacerbation) and three of the six deaths in the salmeterol group resulted from respiratory failure.

DISCUSSION

COPD is, by definition, a disease of airflow limitation. However, the evaluation of patients with COPD is no longer limited to short term improvements in objective measures of airflow but it is also recognised that the progressive physiological impairment will ultimately result in symptoms of breathlessness, limitations in activity, and adverse consequences on health status.

We have compared treatment with tiotropium 18 µg (a once daily inhaled anticholinergic that has its effect through prolonged M₃ receptor antagonism), salmeterol 50 µg twice daily (a long acting inhaled β₂ agonist), and placebo in 1207 patients with COPD. The results indicate that, compared with placebo, tiotropium reduced exacerbations, reduced health resource usage, and improved HRQoL and dyspnoea. Salmeterol, on the other hand, did not have a meaningful impact on exacerbations, HRQoL, or use of health resources compared with placebo except for a higher proportion of patients achieving an improvement in TDI of at least 1 unit. Both active drugs provided improvements in bronchodilation with tiotropium being superior to salmeterol. These results confirm those of earlier trials in which tiotropium has been compared over a 1 year period with placebo and ipratropium.^{14 15}

Several recent publications have highlighted the impact of pharmacotherapy on exacerbations of COPD. Inhaled corticosteroids in the ISOLDE and Lung Health II trials were associated with reduced exacerbations in subpopulations of severe patients.^{5 6} There are few data on the role of bronchodilator treatment in reducing the frequency of COPD exacerbations, although Friedman *et al*⁸ reported that, compared with albuterol, both ipratropium monotherapy and the combination of ipratropium and albuterol decreased exacerbations by 33%. The effect of treatment with long acting β₂ adrenergic bronchodilators on COPD exacerbations has been conflicting.^{9 10} The present study found reductions in exacerbations and associated health care usage. While the data on hospital admissions were generally confirmed by hospital records, data on other treatment visits (apart from those involving the investigator) were based on self-recall and subject to potential under or over reporting. The definition of exacerbations used in this study differs somewhat from other publications. However, the requirement for a minimum time frame (3 days) should have reduced the reporting of simple daily fluctuations in underlying COPD as exacerbations and the definition itself does not necessarily explain the differences in the number of events in the placebo population observed in other reports.^{8–10}

In addition to the somewhat conflicting results for exacerbations, studies on the effect of long acting β₂ adrenergic bronchodilators on other health outcomes in COPD have also provided inconsistent results.^{9 10 20 21} We found that a high proportion of placebo treated patients (39%) had a clinically meaningful improvement in health status. The results of the present trial are consistent, albeit somewhat higher, than

those reported in the tiotropium 1-year placebo controlled trial¹⁴ in which 30% of patients treated with placebo were observed to have an improvement in health status of at least 4 units at the end of the trial. The difference from the present study may reflect the longer duration in the 1-year trials as COPD is associated with a progressive decline in health status.⁵ However, it is possible that the high placebo response may indicate a limitation in the instrument or may reflect a bias related to a population willing to participate in clinical trials.

The mechanism by which bronchodilators might reduce exacerbations and hospital admissions for COPD remains to be defined. A major feature of most COPD exacerbations is an increase in dyspnoea which is often a consequence of the worsening hyperinflation characteristic of advanced COPD.²² Bronchodilators such as β agonists and anticholinergics improve FEV₁ but also improve FVC and can reduce the degree of hyperinflation. Such improvements are also associated with a reduction in dyspnoea in patients with COPD, particularly during exercise.²³

Whatever the underlying mechanism, a symptomatic improvement is likely to alter the patient decision making process—particularly on the need for seeking help—and this may have an impact on the use of health resources. A reduction in the frequency of exacerbations or on the time to exacerbation, for example, would probably be associated with a reduction in the cost of COPD management²⁴ as well as an improvement in the HRQoL of patients.²⁵ Similarly, more stable lung function and symptomatic baseline would be expected to reduce the need for unscheduled physician visits and contacts with healthcare facilities. Whether or not effective and continuous bronchodilation alters the intensity or type of inflammatory response in the airways, which might modulate exacerbations in COPD, is not known. Seemungal *et al* have noted an association between increasing frequency of exacerbations and declining HRQoL.²⁶ Indeed, such a pattern has been documented with tiotropium in previous 1-year trials.²⁵ In this regard, it was interesting to note that tiotropium was associated with a decrease in exacerbations in the current trial. Furthermore, patients receiving tiotropium in this study had the smallest number of days when they were unable to perform their usual daily activities due to poor symptom control.

In the present study both tiotropium and salmeterol improved FEV₁ and FVC. Consistent with the results on health outcomes, the improvements in FEV₁ and FVC with tiotropium were superior to those with either salmeterol or placebo, and these bronchodilator effects were maintained over time. However, there appeared to be tachyphylaxis to the effects of salmeterol. Such a phenomenon with salmeterol has not been shown previously in other published trials, but generally such trials have been of a shorter duration (12–16 weeks).

In summary, we have shown that tiotropium 18 µg once daily is associated with improved dyspnoea, improved bronchodilation, reduced exacerbations, and improvements in HRQoL compared with placebo. The effect of salmeterol on these outcomes was modest compared with placebo and generally was neither clinically nor statistically meaningful.

ACKNOWLEDGEMENTS

We are grateful to the patients and their families, and to the coordinators, nurses, and therapists for their dedication to the study. Financial support for this study was provided by Boehringer Ingelheim Pharmaceuticals.

The following investigators and industry scientists participated in the studies: Dr R Aalbers, Dr T Bantje, Dr E Beck, Dr B Bergholtz, Dr L Bernabeu, Professor R Bonnett, Mr J Bourbeau, Professor D Caillaud, Dr L Clancy, Dr J Creemers, Professor C Criece, Professor R Dahl, Professor Donner, Dr H Damste, Dr J Donohue, Dr P Driesen, Dr J Eckmayr, Dr P Enright, Dr Faurschou, Dr P Firth, Dr F Fortin, Dr J

Garrett, Dr J Goldberg, Dr A Greefhorst, Dr J Grosbois, Dr A Gulsvik, Ms K Gunther, Dr U Harnest, Dr H Harving, Dr R Hendricks, Dr C Hermann, Dr C Hesse, Dr J Ilowite, Dr B Interiano, Dr C Jenkins, Dr C LeMerre, Dr G Johansson, Dr B Johnson, Professor J Joubert, Dr M Kamdar, Dr J Kotaniemi, Professor F Kummer, Dr R Lapidus, Professor Larsson, Dr C Le Merre, Ms A Lee, Dr A Lindqvist, Dr C Marchioni, Professor D McKenzie, Dr M Middle, Dr S Menjoge, Ms A Monckton, Dr J Montserrat, Dr J Morera, Dr M Morgan, Dr S O'Neill, Dr P Paggiaro, Dr K Patel, Dr M Peters, Dr T Pierce, Professor H Rea, Dr O Røfve, Ms K Reilly, Professor Ruffin, Dr C Sanguinetti, Dr T Schaberg, Dr C Serby, Dr J Taylor, Professor T Todisco, Professor P Thompson, Dr J Van Noord, Dr K Venho, Dr N Vetter, Dr J Viljoen, Professor W Vincken, Dr T Witek Jr, Mr W Wólyniec, Dr J Zibrack.

Authors' affiliations

V Brusasco, Facoltà di Medicina e Chirurgia, Università di Genova, Genova, Italy

R Hodder, Ottawa Civic Hospital, Ottawa, Ontario, Canada

M Miravittles, Hospital Universitari Vall Hebron, Servei de Neumologia, Barcelona, Spain

L Korducki, **L Towse**, **S Kesten**, Boehringer Ingelheim Pharmaceuticals, Germany

Supported by Boehringer Ingelheim Pharmaceuticals Inc.

REFERENCES

- 1 **Global Initiative for Chronic Obstructive Lung Disease (GOLD).** *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (executive summary)*. Bethesda, MD: National Institutes of Health, 2001.
- 2 **Friedman M**, Hilleman DE. Economic burden of chronic obstructive pulmonary disease. *Pharmacoeconomics* 2001;**19**:245–54.
- 3 **Belman MJ**, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**153**:967–75.
- 4 **Anthonisen NR**, Manfreda J, Warren C, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;**106**:196–204.
- 5 **Burge PS**, Calverley PMA, Jones PW, et al. Randomised, double-blind, placebo controlled study of fluticasone propionate inpatients with moderate to severe chronic obstructive disease: the ISOLDE trial. *BMJ* 2000;**320**:1297–303.
- 6 **The Lung Health Study Research Group.** Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**:1902–9.
- 7 **Destache CJ**, Dewan N, O'Donohue WJ, et al. Clinical and economic considerations in the treatment of acute exacerbations of chronic bronchitis. *J Antimicrob Chemother* 1999;**43**(Suppl A):107–13.
- 8 **Friedman M**, Witek Jr TJ, Serby CW, et al. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared to ipratropium alone and albuterol alone in chronic obstructive pulmonary disease. *Chest* 1999;**115**:635–41.
- 9 **Mahler DA**, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999;**115**:957–65.
- 10 **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.
- 11 **Koyama H**, Nishimura K, Ikeda A, et al. A comparison of the bronchodilating effects of oxitropium bromide and fenoterol in patients with chronic obstructive pulmonary disease. *Chest* 1993;**104**:1743–7.
- 12 **Barnes PJ**, Belvisi MG, Mak JCW, et al. Tiotropium bromide (Ba 679 Br), a novel long-acting muscarinic antagonist for the treatment of obstructive airways disease. *Life Sci* 1995;**56**:853–9.
- 13 **Disse B**, Speck GA, Rominger KL, et al. Tiotropium (Spiriva): mechanistical considerations and clinical profile in obstructive lung disease. *Life Sci* 1999;**64**:457–64.
- 14 **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.
- 15 **Vincken W**, van Noord JA, Greefhorst APM, et al. Improvements in health status in patients with COPD during one year treatment with tiotropium. *Eur Respir J* 2002;**19**:209–16.
- 16 **American Thoracic Society.** Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med* 1995;**152**:1107–36.
- 17 **Mahler DA**, Weinberg DH, Wells CK, et al. The measurement of dyspnea: contents, interobserver agreement and physiologic correlates of two new clinical indexes. *Chest* 1984;**85**:751–8.
- 18 **Jones PW**, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. *Am Rev Respir Dis* 1992;**145**:1321–7.
- 19 **Schaffer JS.** *Analysis of incomplete multivariate data*. New York: Chapman and Hall, 1997.
- 20 **Jones PW**, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med* 1997;**155**:1283–9.
- 21 **Rutten-van Molken M**, Roos B, Van Noord JA. An empirical comparison of the St George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ) in a clinical trial setting. *Thorax* 1999;**54**:995–1003.
- 22 **O'Donnell DE.** Breathlessness in patients with chronic airflow limitation. Mechanisms and management. *Chest* 1994;**106**:904–12.
- 23 **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.
- 24 **Oostenbrink JM**, Rutten-van Molken M, Koch P, et al. Costs of COPD exacerbations. *Am J Respir Crit Care Med* 2001;**163**:A642.
- 25 **Jones PW**, Koch P, Menjoge SS, et al. The impact of COPD exacerbations on health related quality of life is attenuated by tiotropium. *Am J Respir Crit Care Med* 2001;**163**:A771.
- 26 **Seemungal TA**, Donaldson GC, Paul EA, et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**:1418–22.