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ORIGINAL RESEARCH

Patient-level pooled analysis of the effect of tiotropium on COPD exacerbations and related hospitalisations

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Abstract

Aim: To assess the effect of tiotropium 18mcg once daily on chronic obstructive pulmonary disease (COPD) exacerbations and exacerbation-related hospitalisations using a patient-level pooled analysis.

Methods: All completed randomised, placebo-controlled, parallel-group tiotropium trials with a duration of ≥24 weeks were included (n=9). An exacerbation was defined in each study as ≥2 respiratory symptoms lasting ≥3 days, and requiring treatment with antibiotics and/or systemic steroids and/or hospitalisation.

Results: Compared with placebo (2,862 patients), tiotropium (3,309 patients) significantly reduced by 21% both the risk of COPD exacerbation (95% confidence interval [CI] 0.73–0.86; p<0.0001) and the risk of exacerbation-associated hospitalisation (95% CI 0.65–0.96; p=0.015). Time to first exacerbation and first associated hospitalisation were increased. The protective effect of tiotropium was consistent regardless of age, gender, inhaled corticosteroid use and disease severity.

Conclusion: This analysis provides further confirmatory evidence that tiotropium reduces the risk of exacerbation and associated hospitalisation.

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Keywords COPD, exacerbations, hospitalisations, pooled analysis, tiotropium

Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) accelerate lung function decline,[1] reduce health-related quality of life,[2,3] and increase the risk of hospitalisations and death.[4,5] Hence, prevention of exacerbations is an important treatment goal.[6] Hospitalisation of COPD patients due to an exacerbation is of particular relevance, since patients with a severe exacerbation requiring hospitalisation are at an increased risk of death[4,5,7] and hospital stays are a major driver of healthcare costs.[8,9]

Tiotropium (Spiriva®) has been previously demonstrated to reduce the risk of exacerbations and associated hospitalisations in individual trials as secondary outcomes,[10-14] and more recently as a primary outcome.[15] As these trials were available in the same database, this has provided an important opportunity to assess in more detail the effects of tiotropium on these outcomes in comparison with placebo.

Pooling data from multiple trials has many benefits: it reduces the probability of false negative results, uncertainty and disagreement; it allows the exploration of *a priori* hypotheses regarding treatment effects in subgroups; and it enables exploration of heterogeneity between studies. However, pooled analyses can be prone to inherent biases if there is significant heterogeneity between trials, such as populations, interventions and exacerbation definitions, as well as bias from the publication of only positive trials. This can be overcome if patient-level data from all studies are available and study designs and interventions are the same.

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Table 1. Major entry criteria for studies included in the pooled analysis.

Inclusion criteria	Exclusion criteria
• Diagnosis of stable COPD	• Asthma or any unstable medical condition precluding participation
• Males or females ≥40 years	• Regular use of daytime oxygen therapy
• FEV_1 ≤65% predicted*	• COPD exacerbation or lower respiratory tract infection within 6 weeks‡
• FEV_1 /FVC ≤70%†	• Use of steroids in unstable dose or the equivalent of >10 mg prednisone
• Smoking history ≥10 pack-years	• Recent history of myocardial infarction, unstable arrhythmia, or hospitalisation for heart failure

*≤60% (Studies #205.130 and #205.137[11]) or ≤70% (Study #205.270[17]); †FEV_1/SVC (Study #205.214[12]); ‡4 weeks (Study #205.270[17]).
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SVC, slow vital capacity.

A recent meta-analysis using published data from tiotropium trials found that tiotropium significantly reduced the odds of a COPD exacerbation and related hospitalisation compared with placebo and ipratropium;[16] however, that meta-analysis considered short-term trials in stable COPD not designed to capture drug effects on exacerbations, as well as long-term trials. Furthermore, it used the original heterogeneous definitions of exacerbations across studies. The pooled analysis presented here used the original data for each patient available, which has allowed the standardisation of exacerbation-related objective measures. Thus, it is a patient-level meta-analysis. In addition, the tiotropium studies available for this analysis had similar inclusion criteria and standardised interventions. Our project was planned to assess the overall effect of tiotropium on COPD exacerbations and related hospitalisations compared with placebo, with the robustness of the effect being tested across subgroups.

Methods

Studies included

All randomised, double-blind, placebo-controlled, parallel-group studies with tiotropium 18mcg once daily in COPD patients, with an observation period of ≥24 weeks and completed by 17th February 2006, were included in this pooled analysis (n=9).[10-15,17] At the time of manuscript finalisation, this dataset reflected all completed studies that match the inclusion criteria.

In each study, patients were randomised to either tiotropium 18mcg capsule or placebo powder inhaled via the HandiHaler® in the morning. Short-acting β_2-agonists were allowed as rescue medication to control day-to-day symptoms. All studies allowed inhaled corticosteroids (ICS) at stable doses, and theophyllines at stable doses were allowed in all studies except Trial #205.214.[12] Studies #205.266[15] and #205.259[14] additionally permitted long-acting β_2-agonists.

All trials had common entry criteria (Table 1). Additionally, Study #205.259[14] specified that subjects had a history of exacerbations requiring antibiotics/oral steroids in the last two years, and four trials excluded patients who had undergone rehabilitation in either the last six weeks (Studies #205.130,[11] #205.137,[11] #205.256[13]) or six months (Study 205.259[14]).

Exacerbation definition

In the investigations herein, an exacerbation was defined as ≥2 (increased or new-onset) respiratory symptoms such as cough, sputum, wheezing, dyspnoea, or chest tightness, lasting ≥3 days and requiring treatment with antibiotics and/or systemic steroids and/or hospitalisation. This definition was retrospectively applied to all trials and was the definition used originally in Study 205.266.[15] Exacerbations were determined from records of adverse events or via case report form. All hospitalisations that included COPD exacerbation were considered as exacerbation-related hospitalisations.

Planned analyses

The full analysis set (FAS) consisting of all randomised patients from all trials was included in the pooled analysis. Endpoints were: (1) proportion of patients with COPD exacerbation; (2) proportion of patients with hospitalisation associated with COPD exacerbation; (3) time to first COPD exacerbation; and (4) time to first hospitalisation associated with COPD exacerbation.

Subgroup analyses were conducted according to age (≤65 and >65 years), gender, disease severity and ICS use at baseline. For analysis according to disease severity, patients with a pre-brochodilator forced expiratory volume in 1 second (FEV_1) of ≤50% predicted (ECCS criteria) were considered as having severe to very severe disease, and those with FEV_1 >50% were considered as having moderate disease.

Additional analyses (including all subgroup analyses) were carried out based on alternative definitions of exacerbations of COPD. These definitions were essentially the same, but were limited to only those exacerbations treated with antibiotics, or only those treated with systemic corticosteroids. Analyses of exacerbations associated with pneumonia and fatal exacerbations were also conducted.

Although Study #205.230[18] had a 24-week observation period, it was decided not to include this study in the pooled analysis as patients underwent pulmonary rehabilitation alongside tiotropium or placebo treatment. However, to ensure that the addition of this study did not alter the conclusions, analyses were repeated after inclusion of this study.

Statistical methods

Stratified Cox regression was used to compute hazard ratios

Table 2. Baseline characteristics for the nine studies included in the pooled analysis (n=6171).

Study #	205.114/117[10]	205.115/128[10]	205.130[11]	205.137[11]	205.214[12]	205.256[13]	205.259[14]	205.266[15]	205.270[17]
Duration weeks	48	48	24	24	48	36	48	24	48
Patients (n)	470	451	410	392	1010	554	913	1829	142
Males (%)	65.3	64.7	74.4	79.3	87.8	86.1	59.8	98.5	62.7
Mean age (y)	65.2	65.2	65.0	63.3	64.8	64.2	66.8	67.9	66.4
Mean FEV_1 (L)	1.02	1.03	1.09	1.13	1.37	1.36	0.96	1.04	1.29
Mean FEV_1 (% pred)	36.8	37.1	38.6	39.3	48.9	47.1	37.7	33.5	49.2
Mean FVC (L)	2.23	2.32	2.56	2.63	2.56	2.50	2.11	2.17	2.22
Mean FEV_1/FVC (%)	46.2	45.1	42.5	43.4	54.6	54.3	46.3	47.8	58.6

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; pred, predicted.

Figure 1. Hazard ratio for an exacerbation of COPD in the tiotropium group compared with the placebo group (Cox Proportional-Hazard Approach).

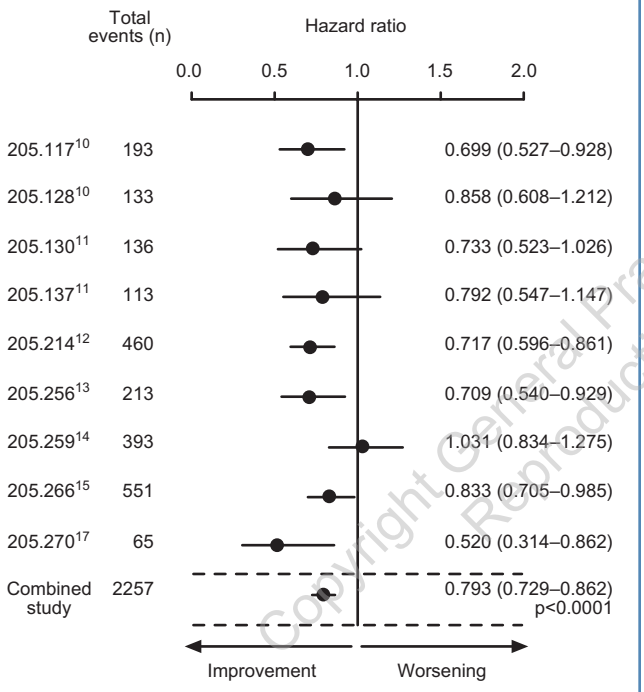
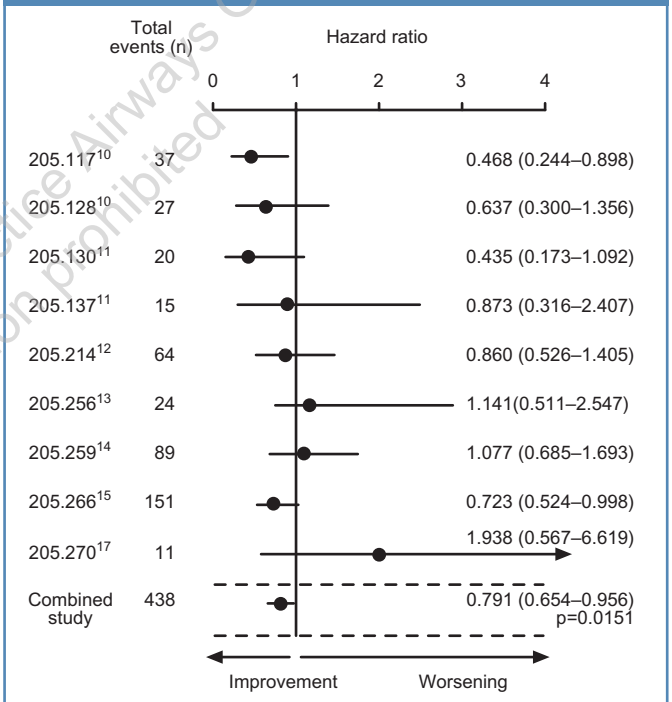


Figure 2. Hazard ratio for an exacerbation-associated hospitalisation of COPD in the tiotropium group compared with the placebo group (Cox Proportional-Hazard Approach).



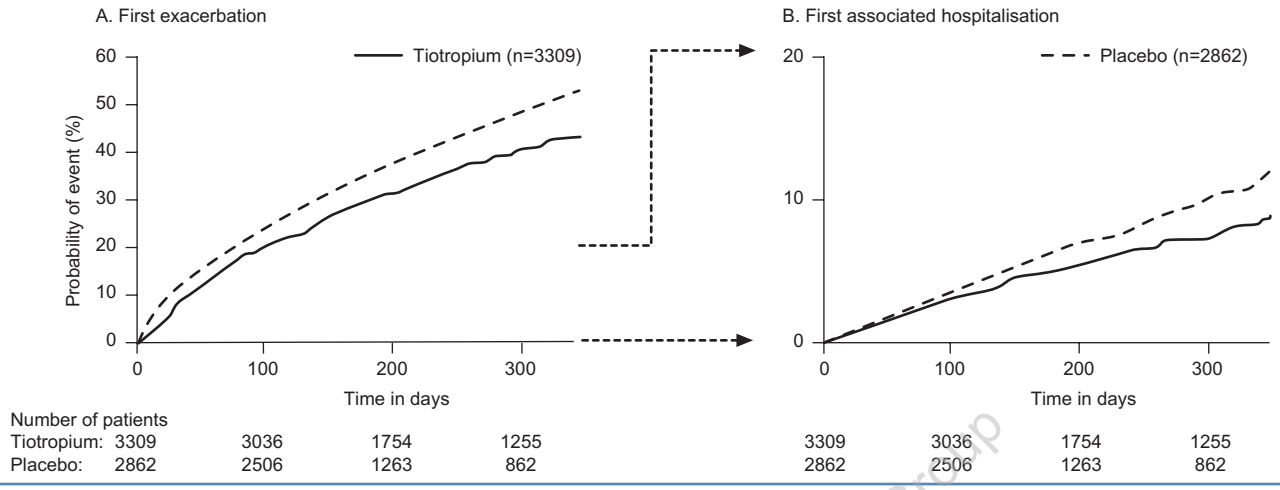
of tiotropium compared with placebo using trial as a stratum. By-trial Cox regression analysis was also conducted and 95% confidence intervals (CIs) provided for the hazard ratios.

Sensitivity analyses, crude incidence rates and exposure-adjusted incidence rates (since studies were subject to different durations and rate of premature withdrawal) were also provided. Exposure was defined as the cumulative time that patients were in the study from randomisation until either the onset of an event or the discontinuation of treatment. In Study 205.266,[15] patients were followed up for the duration of the study even after they discontinued treatment. For that study, if a patient did not have an event, the last day of participation was used in place of the last day of treatment. The Cochran-Mantel-Haenszel procedure, using study as stratum, was used to compare the two treatment groups.

An exacerbation leading to hospitalisation was included in the analysis if the exacerbation started during the observation time. Hence, a patient who experienced an exacerbation and was withdrawn from the study due to this event, but subsequently hospitalised for this exacerbation, was counted in the hospitalisation analysis, even though the hospitalisation occurred after the end of the observation period for this patient.

Time to COPD exacerbation and hospitalisation associated with exacerbation are displayed using cumulative incidence rates based on Kaplan-Meier estimates of probability of no event. Plots were truncated to 46 weeks, at which time a

Figure 3. Kaplan-Meier estimates of the probability of: (a) exacerbation and (b) exacerbation-associated hospitalisation.



substantial number of patients still received study drug – though the analyses were conducted using the entire dataset.

Results

Patient disposition

A total of 6,171 patients were included (3,309 tiotropium and 2,862 placebo). Of these, 1,403 (22.7%) discontinued early (626 [18.9%] in the tiotropium group and 777 [27.1%] in the placebo group). The main reported reasons for early withdrawal were worsening of COPD/lack of efficacy (9.9% in the tiotropium group and 16.1% in the placebo group). The mean age of the patients was 66 years; 81% were male, and 68% had stopped smoking prior to randomisation. The mean smoking history was 54.7 pack-years and mean body mass index (BMI) was 26.7. Mean COPD duration was 9.8 years, mean percentage predicted FEV_1 was 39.5% and FEV_1/forced vital capacity (FVC) was 48.6%. Patients were balanced with respect to demographics and other baseline characteristics across the two treatment groups. Selected details for individual studies are shown in Table 2.

Risk of exacerbation

Stratified Cox regression showed that tiotropium significantly reduced the risk of COPD exacerbation by 21% (hazard ratio of 0.79) compared with placebo (Figure 1; p<0.0001). The 95% CI for the hazard ratio was 0.73–0.86, which equates to a reduction of risk from 14–27%. Figure 1 shows that the reduction in hazard ratio with tiotropium compared with placebo was consistent in eight out of nine studies, which had a range of hazard ratio from 0.52–0.86. In Study 205.259, the hazard ratio was 1.03.

Analysis of crude rates of exacerbations between tiotropium and placebo groups showed a rate ratio of 0.87 (95% CI 0.82–0.93). Adjusting for the greater numbers of early withdrawals in the placebo groups in all trials, the rate ratio for exacerbation incidence was 0.78 (22% reduction compared with placebo; 95% CI 0.72–0.85).

There were very few fatal exacerbations (<0.5%). The number of fatal exacerbations was 17 (6 in the tiotropium group and 11 in the placebo group). The stratified Cox regression for fatal exacerbations resulted in a hazard ratio (tiotropium vs placebo) of 0.45 (95% CI 0.16–1.22).

Risk of exacerbation-associated hospitalisation

Stratified Cox regression showed that tiotropium significantly reduced the risk of hospitalisation associated with COPD exacerbation compared with placebo (Figure 2; p=0.015). The hazard ratio was 0.79 (21% reduction compared with placebo; 95% CI 0.65–0.96). Figure 2 shows that the hazard ratio for hospitalisation associated with COPD exacerbation of tiotropium with placebo was <1 in six out of nine studies.

The rate ratio between tiotropium and placebo for crude rates was 0.84 (16% reduction compared with placebo; 95% CI 0.70–1.00). Using an exposure-adjusted approach, the relative risk of incidence was 0.79 (21% reduction compared with placebo; 95% CI 0.65–0.96).

Time to first exacerbation and first associated hospitalisation

Figure 3A displays the cumulative incidence rates for COPD exacerbation over time based on Kaplan-Meier procedure. It shows a separation between tiotropium and placebo (p<0.001). The cumulative incidence rate of COPD exacerbation at 46 weeks, when a substantial number of patients still received the study drug, was 42.1% for tiotropium compared with 50.8% for placebo.

A separation between tiotropium and placebo is similarly shown in Figure 3B for the cumulative incidence rates for hospitalisation associated with COPD exacerbation over time based on Kaplan-Meier procedure (p=0.015). The cumulative incidence rate of hospitalisations associated with COPD

Table 3. Relative risk of an exacerbation-associated hospitalisation in the tiotropium group compared with the placebo group according to baseline age, gender, ICS use and FEV_1.

	Tiotropium (n)	Placebo (n)	HR	95% CI
Age ≤65 years	1496	1241	0.717	0.525–0.980
Age >65 years	1813	1621	0.848	0.668–1.078
Male	2659	2357	0.766	0.622–0.944
Female	650	505	0.868	0.546–1.378
ICS user	1885	1581	0.790	0.627–0.994
Non-ICS user	1424	1281	0.778	0.557–1.087
FEV_1 ≤50%	2507	2164	0.751	0.613–0.920
FEV_1 >50%	800	696	1.056	0.619–1.802

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; ICS, inhaled corticosteroid.

Table 4. Hazard ratios and 95% CIs for with-pneumonia exacerbations.

Study #	Total events (n)	HR	95% CI
205.114/117[10]	22	0.509	0.220–1.178
205.115/128[10]	19	0.660	0.268–1.624
205.130[11]	6	4.130	0.483–35.354
205.137[11]	8	0.998	0.250–3.991
205.214[12]	0	NA	NA
205.256[13]	0	NA	NA
205.259[14]	55	1.385	0.755–2.540
205.266[15]	72	0.555	0.343–0.898
205.270[17]	2	1.082	0.068–17.295
Combined studies	184	0.789	0.588–1.058

CI, confidence interval; HR, hazard ratio; NA, not available.

exacerbation at 46 weeks was 8.5% for tiotropium compared with 10.8% for placebo.

Subgroup analyses

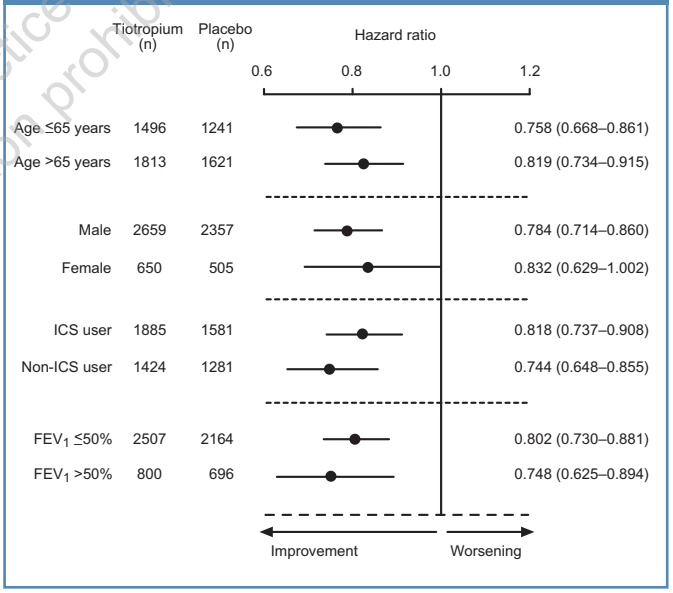
Older age, being female, concomitant ICS use, and low FEV_1, are all associated with a tendency for an increased risk of an exacerbation. However, the risk of an exacerbation in the tiotropium group compared with the placebo group was reduced irrespective of stratification of patients according to these subgroups (Figure 4). Hospitalisation results were also consistent across these subgroups, with the exception of the risk of exacerbations requiring hospitalisation in patients with less advanced disease (FEV_1 >50%), who were rarely hospitalised for these events (Table 3).

Additional sensitivity analyses

Figure 5 shows the hazard ratios of exacerbation using alternative treatment definitions for an exacerbation (exacerbations treated with antibiotics and those treated with systemic corticosteroids). The risk for exacerbations treated with antibiotics was generally higher than for those treated with corticosteroids. The ratio was approximately 3:2, without a recognisable pattern across studies, geographical regions, patient subgroups, or assignments to tiotropium or placebo. Overall, tiotropium significantly reduced the risk of an exacerbation in each exacerbation treatment subgroup (rate ratios of 0.82 and 0.75, respectively). Hospitalisation results in these subgroups were also consistent with those obtained for the exacerbations; the hazard ratio (tiotropium vs placebo) was 0.82 (95% CI 0.75–0.89) for those requiring antibiotics and 0.75 (95% CI 0.67–0.83) for those requiring oral corticosteroids.

Since pneumonias qualified under the definition of exacerbation used in the main analysis, analyses were conducted to compare the incidence of reported pneumonia

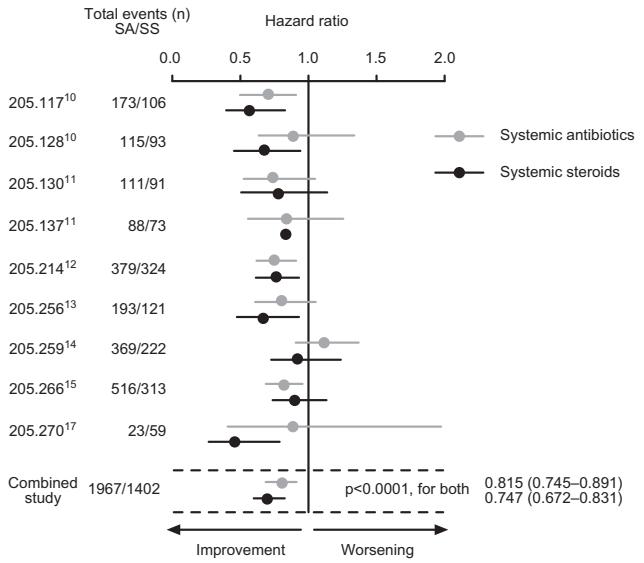
Figure 4. Relative risk of an exacerbation event in the tiotropium group compared with the placebo group according to baseline age, gender, ICS use and FEV_1.



across treatment groups. Table 4 shows that the incidence of pneumonia tended to be reduced by 21% (not statistically significant) for tiotropium compared with placebo. The stratified Cox regression resulted in a hazard ratio of 0.79 (95% CI 0.59–1.06). Overall, <5% of patients were reported as having pneumonia.

Addition of Study 205.23018 (in which patients underwent pulmonary rehabilitation alongside tiotropium or placebo treatment) and repeat of the entire analysis did not alter qualitatively and did not significantly alter quantitatively any of the results.

Figure 5. Hazard ratio for an exacerbation (by intervention).



Discussion

In this patient-level pooled analysis of all completed randomised placebo-controlled long-term COPD trials with tiotropium 18mcg capsules, active treatment significantly and effectively reduced the proportion of patients with exacerbations by 21%. Of note, the protective effect of tiotropium was not confined to moderate exacerbations, but was similarly observed with regard to most severe exacerbations, as defined by those requiring hospitalisation. Subgroup analyses by patient age, gender, concomitant use of ICS and severity of underlying COPD, and additional sensitivity analyses with varying definitions of exacerbations, as well as an explorative risk estimation for pneumonia and fatal exacerbations, underline the broad scope of these findings.

Although the design of the individual trials was similar with regard to inclusion/exclusion criteria, there were differences in the data acquisition modalities, time between visits, trial durations, follow-up of withdrawn patients, original definitions of exacerbations, and the populations studied. In this analysis, the definition of exacerbation was standardised, with one definition[15] applied to all studies. This definition is similar to that used in other COPD studies evaluating alternative treatment options.[19-21] Tiotropium reduced the proportion of patients with exacerbations in eight out of nine studies, with effect sizes ranging from a 48% reduction[17] to a 3% excess.[14] The risk reduction was fairly homogeneous across studies with the exception of the trial showing a 3% excess.[14] The reasons for this outlier study remain unclear. This trial had longer (18-week) intervals between visits without interim phone calls or patient record cards; therefore, there may have been under-reporting of exacerbations in this trial, which recruited a large number of patients with advanced COPD. We included this study in the sense of a worst-case approach. At the other extreme, the most positive study[17] was conducted at a single centre specialising in COPD exacerbations that used sophisticated patient record cards for documentation.

The risk reduction for exacerbation-associated hospitalisation appeared less consistent across studies than the risk reduction for exacerbations, even though the effect size was comparable. There are several challenges associated with evaluation of this endpoint. Firstly, hospitalisation for COPD is an infrequent event, compared with exacerbation of COPD in general. The greatest confidence interval was seen with Study #205.270, which was based on only seven events with tiotropium compared with four events with placebo. Secondly, patients may be withdrawn from a study due to deterioration of their disease, thus preventing the consideration of an imminent hospitalisation for the analysis. Thirdly, patients may die from a severe exacerbation at home prior to being admitted to hospital.[22]

A recent meta-analysis by Barr *et al*.[16] evaluating efficacy of tiotropium in COPD patients considered short-term and active-controlled trials (n=9). It included 8,002 patients, approximately 3,276 patient-years in placebo-controlled trials and used the original heterogeneous definitions of exacerbations across studies. They found that tiotropium reduced the risk ratio of a COPD exacerbation (0.73; 95% CI 0.66–0.81) and related hospitalisation (0.68; 95% CI 0.54–0.84) compared with placebo and ipratropium. Our study relies on randomised, placebo-controlled, long-term studies with 6,171 patients (approximately 4,080 patient-years of exposure to tiotropium or placebo). Advantages of our pooled analysis are the completeness of studies included following systematic selection criteria, and the full access to the raw dataset of the tiotropium 18mcg clinical development programme, which allowed a homogeneous definition of exacerbations and associated hospitalisations across studies. Despite the differences in data and methodology, both pooled/meta-analyses found statistically significant reductions of >20% in the proportion of patients with exacerbations, and a similar reduction in patients hospitalised due to an exacerbation. This indicates that inclusion of short-term trials with stable patients by Barr *et al.*[16] did not bias the results, selective publication of positive studies only did not occur, and use of heterogeneous definitions of endpoints did not affect the robust treatment effect. Findings from randomised controlled trials are complemented by results from a recent case-control study supporting efficacy of tiotropium in a real-life setting.[23]

Our analysis, which accommodates all available long-term data with tiotropium 18mcg once daily to date and which provides level 1A evidence on tiotropium efficacy,[24-26] is

complemented by the 4-year data from the UPLIFT® (Understanding Potential Long-term Impacts on Function with Tiotropium) study on almost 6,000 patients published in late 2008.[27] This trial showed that tiotropium was associated with a 14% reduction in COPD exacerbations and associated hospitalisations. This reduction is smaller than that observed in our pooled analysis and may have been influenced by the high rate of prescriptions for concomitant respiratory medications (72% taking long-acting β_2-agonists and 74% taking ICS at some time during the treatment period) in that study.

In our analysis, tiotropium reduced the exposure-adjusted incidence of exacerbations by 21%. This reduction is consistent with reductions in yearly numbers of exacerbations with other drugs from different trials, such as fluticasone propionate (25% reduction vs placebo),[28] budesonide/formoterol (24%),[21] and salmeterol/fluticasone combination (25%[29] and 25%[20]). However, these trials had different outcome parameters, definitions of exacerbations, patient populations, lengths, and other study parameters, which makes comparison across trials inappropriate. Also, counting of multiple events per patient poses problems regarding the independence of consecutive exacerbations.[22] Nevertheless, a comparison of exacerbation rate within the same trial has suggested that tiotropium is similarly effective to a two-drug combination (salmeterol/fluticasone).[30] We believe that the treatment effect on exacerbations can best be evaluated by the endpoint used in our study (i.e. quantifying the proportion of patients with exacerbations/hospitalisations), since a subgroup of strong responders could mimic a general treatment effect in the overall population studied[19] if the number of events was utilised; this would not occur in a comparison of the proportion of patients with an event in a reasonable timeframe.

The main strengths of our study are: a large cohort of patients (allowing robust subgroup analyses); high-quality data (ensured by the individual trials that followed similar designs and were conducted according to GCP/ICH); patient-data level analysis (which ensured a thorough and homogeneous analysis using the retrospectively applied exacerbation definition); and the incorporation of early withdrawals through Cox regression. The study selection for the analysis followed pre-specified rules that excluded short-term trials and included long-term trials, and data were handled in a standardised manner.

However, although data were collected prospectively, the analysis was done *post hoc*. Information about exacerbations had to be drawn from adverse event reports in some studies, but was collected on specific clinical trial report form pages in others. While the former mode of exacerbation data collection imposes some risk of underreporting, the authors believe that the used definition of exacerbations – essentially a hybrid considering both symptom aspects (from adverse event reports), a minimum duration (at least three days) to exclude day-to-day variation, and health resource information (concomitant medication reports) – ensured capture of the majority of relevant events even from studies that did not focus on exacerbation outcomes. For the same reason, we believe that it was appropriate to waive an adjudication committee (which has been otherwise recommended)[22] in this post hoc analysis. Additionally, inclusion of reported pneumonia that met the COPD exacerbation definition[31] supported complete consideration of relevant events. In contrast, our definition of exacerbations avoided counting mild events that might otherwise have overestimated effects.

In all but one study,[15] there was no follow-up of patients after premature withdrawal beyond a short post-study interval. This approach of "on-treatment analysis" may have missed some exacerbation events in patients who dropped out prior to an exacerbation that occurred during the scheduled observation period.[32] This potential undercounting applied to both treatment groups, and exacerbations that led to premature withdrawal of a patient from the study were still considered for the analysis. Nevertheless, discontinuation in such clinical trials is non-random with a higher rate observed in the groups not receiving tiotropium. This "healthy survivor" phenomenon would tend to underestimate the efficacy of tiotropium in a clinical trial. Finally, hospitalisations associated with an exacerbation were captured even if the patient was withdrawn from the study due to the event, because the starting date of the underlying exacerbation determined counting of the hospitalisation, and because these adverse events were followed up until resolution, final outcome, or death. Additionally, patients with a severe exacerbation who were not hospitalised, and subsequently died at home due to this event, might have caused a bias to the analysis of hospitalisation endpoints. However, it is unlikely that this potential bias overestimated the protective effects of tiotropium, since the explorative risk analysis of a fatal exacerbation episode revealed a non-significant trend in favour of tiotropium.

In summary, the cumulative evidence from long-term clinical trials with tiotropium 18mcg capsules in COPD confirms the observation from individual studies that tiotropium reduces exacerbations and related hospitalisations in COPD during up to one year of treatment. The reduction in the risk for an exacerbation was independent from the clinical character and severity of the exacerbation, the severity of the underlying COPD, concomitant ICS use, age and gender. The effect size of approximately 20% is considered meaningful for patients, physicians and payers, particularly for severe exacerbations requiring hospitalisations. In conclusion, maintenance therapy with tiotropium is an appropriate first-line

therapy for the prevention of exacerbations in patients with COPD. UPLIFT® has provided further promising insights into the efficacy of tiotropium beyond one year of treatment.[27]

Conflict of interest declaration

Dr D Halpin has received reimbursement for attending a symposium and a fee for speaking from Boehringer Ingelheim GmbH and Pfizer Inc. Drs S Menjoge and K Viel are both employees of Boehringer Ingelheim GmbH, the manufacturer of tiotropium (Spiriva®).

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