CORRESPONDENCE

Thorax editorial by Jenkins and Beasley related to tiotropium respimat

We thank Drs Jenkins and Beasley for their comments in the recent editorial regarding tiotropium (SPIRIVA)[1]. Preceding the Singh *et al*[2] analysis cited by the authors, Boehringer Ingelheim (BI) had analysed both the tiotropium HandiHaler and Respimat pooled datasets using patient-level data on-treatment as well as including vital status. The results showed a nominally statistically significant reduction for tiotropium HandiHaler and a numerical increase with tiotropium Respimat compared with the respective placebo group for all-cause mortality.

These results are adequately reflected in the local SPIRIVA product information (http://www.medicines.org.uk/EMC/search results.aspx?term=spiriva&searchtype=QuickSearch).

Recently published analyses on tiotropium Respimat data (including the analyses of Dong *et al*[3]) were conducted on the same set of clinical data; therefore, they cannot be considered independent evidence, and are all limited by not using patient-level data.

The tiotropium Respimat dose (5 μg once daily) was chosen to match the efficacy and safety of the well-established tiotropium HandiHaler 18 μg. Three pharmacokinetics (PK) studies compared the PK of tiotropium after inhalation from both devices. One study[4] found 22% and 35% higher exposures (area under the curve from 0 to 6 h (AUC_{0-6}) and maximum plasma concentration (C_{max})) for Respimat 5 μg versus HandiHaler 18 μg. A second study[5] in Japanese patients showed virtually identical plasma levels. A newly available third study,[6] with optimised procedures for PK analysis, reported 24% and 19% lower exposures (AUC_{0-6} and C_{max}) for tiotropium Respimat 5 μg versus tiotropium HandiHaler 18 μg. This study also demonstrated similar PK variability for the two tiotropium formulations. Therefore, available data suggest similar systemic exposure for both devices and any apparent difference between formulations remains unexplained and implausible. In order to confirm the hypothesis of no difference between matching formulations, BI is conducting the TIOSPIR study in over 17 000 patients comparing once-daily tiotropium Respimat 5 μg and tiotropium HandiHaler 18 μg with all-cause mortality and COPD exacerbations as co-primary endpoints. A further arm with tiotropium Respimat 2.5 μg is included in order to inform dose selection for future combination products. The study is supervised by an independent Data Safety Monitoring Board (DSMB) with access to fully unblinded data. The DSMB evaluates the most current database every 4 months and has, up to now, recommended to 'continue as planned'. The study is approaching finalisation in 2013 and has exceeded three-quarters of the number of events used in the power calculation for the primary analysis.

Finally, the patients enrolled in the tiotropium trial programme had a comorbidity profile comparable with the general COPD population (see online supplement).

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Do Patients in Tiotropium Clinical Trials in COPD Reflect Clinicians Reality? An Analysis of a Pooled Clinical Trial Database

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Abstract

Background: The external validity of clinical trials is frequently challenged. Chronic obstructive pulmonary disease (COPD) patients have substantial comorbidities that need to be considered by physicians when choosing treatments for COPD. Based on epidemiological studies, examples of comorbid conditions with a high prevalence in COPD patients include hypertension (40-55%), ischemic heart disease (10-20%), hypercholesterolemia (35-52%), diabetes (13-25%), anxiety and depression (8-39%). Therefore, it is important to know whether patients with comorbidities were adequately represented in clinical trials, or whether they were deselected by exclusion criteria or simply not recruited in sufficient numbers.

Methods: The analyzed database contains pooled data from 26 placebo-controlled tiotropium HandiHaler® trials of at least 4 weeks' duration. At baseline, physicians recorded the patients' concomitant diseases and relevant medical history within the past 5 years. Medical Dictionary for Regulatory Activities (MedDRA) version 11.1 was used for the coding of the investigator-reported medical diagnoses. In the Understanding the Potential Long-term Impacts on Function with Tiotropium (UPLIFT®) trial, which contributed the largest portion of patients to the database population, relevant exclusion criteria were: a history of asthma, significant other lung diseases (eg, known active tuberculosis, cystic fibrosis, etc), myocardial infarction within the previous 6 months, unstable or life-threatening cardiac arrhythmia, hospitalization for heart failure within the previous year, pulmonary resection, treatment for malignancy within the last 5 years (except for treated basal cell carcinoma) and symptomatic benign prostatic hyperplasia uncontrolled by medication.

Results: In total 17,014 COPD patients were included in this analysis. 76% of the patients were men, 84.4% were of Caucasian origin, the mean age was 64.6 years and the baseline mean forced expiratory volume in 1 second predicted was 41%. Baseline comorbid condition information was available for 15,375 patients. Overall, 90.4% of the patients had concomitant diseases at baseline. The five most frequently affected system organ classes were vascular disorders (44.0%), including hypertension (38.7%), musculoskeletal and connective tissue disorders (35.2%), gastrointestinal disorders (32.6%), metabolism and nutrition disorders (28.8%), and cardiac disorders (26.5%). Frequently occurring conditions at baseline were hypertension (38.7%), conditions suggestive of ischemic heart disease (15.6%), hypercholesterolemia and/or hyperlipidemia (16.7%), diabetes mellitus (9.8%), and anxiety and/or depression (13.7%).

Conclusion: The pattern of percentages of comorbidities among patients included in the 26 tiotropium HandiHaler® clinical trials matches the majority, but not all (eg, for hypercholesterolemia/hyperlipidemia), of the percentages observed in the epidemiological studies. Therefore, this patient population appears to be fairly representative of the general population regarding their comorbid conditions.

Introduction

Patient populations in clinical trials are subject to inclusion and exclusion criteria. This selectivity is important in order to determine the comparative efficacy and safety, while limiting the potential for confounding by including too broad a population. However, as a consequence of the inclusion and exclusion criteria, it is often assumed that the patients entering clinical trials would be highly selected and their characteristics as well as concomitant treatment regimens would not reflect regular clinical practice. Hence, the external validity of clinical trials is occasionally challenged.[1-3] Epidemiological or observational studies can provide a broader perspective on the background, comorbid conditions, treatment patterns, and outcomes of patients in clinical practice.

Patients with chronic obstructive pulmonary disease (COPD) frequently have multiple comorbid conditions that need to be considered by physicians when choosing treatments for COPD. Either the drug itself might have side effects that could potentially aggravate existing comorbidities or might interfere with treatments for these comorbidities. According to recently published epidemiological studies, examples of comorbid conditions with a high prevalence in COPD patients include hypertension (40-55%), ischemic heart disease (10-20%), hypercholesterolemia (35-52%), diabetes (13-25%), and anxiety and depression (8-39%).[4-6] Therefore, it is important to know whether patients with comorbidities are adequately represented in clinical trials of COPD, or whether they are deselected by exclusion criteria or simply not recruited in sufficient numbers.

Objectives

- To evaluate the baseline characteristics of a pooled group of COPD patients who participated in 26 placebo-controlled tiotropium clinical trials.
- To compare this patient population with those reported in epidemiological studies of COPD.

Method

- Data on patient baseline characteristics were taken from the pooled database (Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany) of 26 completed (as of March 2009) tiotropium HandiHaler® clinical trials.

Study designs of the pooled trials

- The inclusion criteria for the trials were: randomized, placebo-controlled, double-blind, parallel-group design, of ≥4 weeks' duration, assessing tiotropium 18 µg (once daily) given via the HandiHaler® device, for COPD indication. The Boehringer Ingelheim studies of the 26 trials were numbered as follows: #205.114/117, #205.115/128, #205.123, #205.124, #205.130, #205.131, #205.137, #205.214, #205.215, #205.218, #205.223, #205.230, #205.235, #205.247, #205.256, #205.257, #205.259, #205.266, #205.269, #205.270, #205.276, #205.281, #205.282, #205.284, #205.294, #205.301.
- Written informed consent was obtained from all patients and ethics committees approval was obtained for all protocols.
- In principle, trials used similar inclusion and exclusion criteria for patients. Later trials were modified to incorporate slightly more liberal criteria:
  - Inclusion criteria were: diagnosis of COPD, forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio ≤70%, age >40 years, >10 pack-years smoking history.
  - Important exclusion criteria were: diagnosis of asthma, symptomatic prostatic hypertrophy or bladder neck obstruction, narrow-angle glaucoma and known hypersensitivity to study medication or components. Significant disease other than COPD which could significantly confound the study results or preclude study completion was also an exclusion criterion. Other exclusion criteria in earlier trial protocols were heart failure resulting in a hospitalization in the previous 3 years, cardiac arrhythmia requiring drug treatment, or myocardial infarction (MI) within the past year. Nevertheless, heart failure and ischemic heart disease were not necessarily exclusion criteria. Cardiac exclusion criteria were liberalized in more recent trials such as the Understanding the Potential Long-term Impacts on Function with Tiotropium (UPLIFT®) trial (study #205.235) (Table 1). Drug therapy for arrhythmias was permitted provided that the therapy was stable and the patient did not have a history of a life-threatening arrhythmia or pacemaker insertion. In addition, the criterion for recent MI was decreased to 6 months (compared with 1 year in the early trials).
  - Trials #205.131 and #205.223 focused on symptom-limited cardiopulmonary exercise testing and excluded patients over 70 years old. A clinical trial amendment during trial #205.223 increased the upper age limit to 75 years.

Table 1. *Key exclusion criteria in the UPLIFT® trial*

- Recent history (6 months or less) of MI
- Any unstable/life-threatening cardiac arrhythmia or cardiac arrhythmia that required intervention or change in drug therapy within the year prior to enrollment
- Hospitalization for heart failure (New York Heart Association Class III or IV) within the year prior to enrollment
- Known active tuberculosis
- History of asthma, cystic fibrosis, bronchiectasis, interstitial lung disease, or pulmonary thromboembolic disease
- History of thoracotomy with pulmonary resection
- Patients who planned to undergo lung transplant or lung volume reduction surgery
- Malignancy for which patient had undergone resection, radiation therapy, or chemotherapy within the last 5 years. Patients with treated basal cell carcinoma were allowed
- Respiratory infection or exacerbation of COPD in the 4 weeks prior to screening or during the baseline period
- Known hypersensitivity to anticholinergic drugs, lactose, or any other components of the inhalation capsule delivery system
- Patients with known moderate-to-severe renal impairment
- Patients with known narrow-angle glaucoma
- Patients with significant symptomatic prostatic hyperplasia or bladder-neck obstruction (unless symptoms controlled by treatment)
- Significant diseases other than COPD which, in the opinion of the investigator, may have put the patient at risk, or have influenced the study results or the patient's ability to participate in the study
- Use of oral corticosteroid medication at unstable doses (ie, <6 weeks on a stable dose), or at doses ≥10 mg/day

- Use of theophyllines, inhaled corticosteroids (ICS), modest daily doses of oral corticosteroids (provided the dosing was stable) and short-acting β-agonists (SABAs) were permitted in all trials. The 4-year UPLIFT® trial (#205.235; 5992 patients), trial #205.259, trial #205.266 (1829 patients), #205.270, #205.282, and #205.284 also permitted use of long-acting β-agonists (LABAs) as prescribed.

Definitions of comorbidities

- The Medical Dictionary for Regulatory Activities (MedDRA) version 11.1 was used to code relevant medical history/concomitant diagnoses (within the past 5 years) as reported by the investigator at baseline; specific terms (preferred terms [PT]) were categorized under system organ classes (SOC) within MedDRA.
- For conditions that are known to have a high prevalence in COPD patients, MedDRA PTs denoting similar conditions were grouped together (ie, pooled). Table 4 only displays applicable PTs with at least one case.

Results

- The pooled number of COPD patients in the 26 HandiHaler® studies was 17,014.
- As the individual trials had different focuses, certain information was only available for subsets of patients. For example, information on concomitant medication at baseline was recorded in all but one trial (Boehringer Ingelheim trial #205.257) and thus represents a subset of 15,375 patients.
- Health-related quality of life status at baseline, as measured by the St George's Respiratory Questionnaire, was recorded for 10,029 patients of the total population and reversibility testing was performed in another subset of 8366 patients.
- The baseline characteristics of the population were balanced between the tiotropium and the placebo (control) groups (Table 2). Of the total population, 76.0% of patients were men, 84.4% were of Caucasian origin, the mean age was 64.6 years and mean prebronchodilator FEV_1 was 41% predicted normal.

Table 2. *Baseline characteristics of patients in the 26 pooled tiotropium HandiHaler® trials*

Characteristic	Total (N=17,014)
Mean age, years (SD)	64.6 (8.8)
Age ranges in years, n (%)	
<60	4792 (28.2)
60 to <70	6884 (40.5)
≥70	5338 (31.4)
Gender, n (%)	
Male	12,928 (76.0)
Female	4086 (24.0)
Race, n (%)	
White/Caucasian	14,352 (84.4)
Black	494 (2.9)
Asian	413 (2.4)
Not available	1755 (10.3)
Smoking history, n (%)	
Ex-smoker	11,313 (66.5)
Smoker	5690 (33.4)
GOLD Stage, n (%)	
I + II	4542 (26.7)
III	8311 (48.8)
IV	3977 (23.4)
Mean FEV_1, L (SD)	1.16 (0.46)
Mean FEV_1, % predicted (SD)	41.1 (14.2)
Mean FVC, L (SD)	2.48 (0.81)
Mean FVC, % predicted (SD)	69.4 (19.0)
FEV_1/FVC ratio, (SD)	0.47 (0.12)
Reversibility to SABA, n (%)*	
Yes	4131 (49.4)
No	4012 (48.0)
Unknown	223 (2.7)
SGRQ total score, mean (SD)†	46.01 (17.07)

*Data available for a total of 8366 patients. Percentages refer to this number. Reversibility response: reversibility ≥12% and ≥200 mL difference between postbronchodilator FEV_1 and prebronchodilator FEV_1

†Numbers based on 10,029 evaluable patients.

SD, standard deviation; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SABA, short-acting β-agonist; SGRQ, St George's Respiratory Questionnaire

- Approximately 50% of the patients had Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III COPD, with approximately 25% of patients with each of GOLD stage I-II and GOLD stage IV disease.
- The majority of patients (85.3%) were receiving respiratory medications at baseline (Table 3); anticholinergics (including short- and long-acting agents), LABAs, and SABAs were each being received by close to 40% of patients, and ICS by 55% of patients.

Table 3. *Baseline concomitant respiratory medications in the 26 pooled tiotropium HandiHaler® trials*

Commonly received concomitant respiratory medication	Patients, % (N=17,014)
Any concomitant respiratory medication	**85.3**
Anticholinergics	
Long-acting	1.1
Short-acting	40.2
ICS	55.4
Steroids (non-inhaled)	
Oral	3.9
Other	3.0
LABA (inhaled)	38.5
SABA (inhaled)	36.6
Theophylline	19.1
Mucolytic	5.1

Fixed combination medications are listed twice, once under each individual product. Patients could have received ≥1 concomitant medication.

ICS, inhaled corticosteroid; LABA, long-acting β-agonist; SABA, short-acting β-agonist

Comorbid conditions

- Overall, 90.4% of the patients had comorbid conditions or diseases at baseline.
- The five most frequently affected SOCs were vascular disorders (44.0%), musculoskeletal and connective tissue disorders (35.2%), gastrointestinal disorders (32.6%), metabolism and nutrition disorders (28.8%), and cardiac disorders (26.5%) (Table 4).

Table 4. *The 10 most frequent SOCs affected by comorbid conditions in the 26 pooled tiotropium HandiHaler® trials*

SOC	Patients, % (N=15,375)
Total with concomitant diagnoses	90.4
Vascular disorders	44.0
Musculoskeletal and connective tissue disorders	35.2
Gastrointestinal disorders	32.6
Metabolism and nutrition disorders	28.8
Cardiac disorders	26.5
Infections and infestations	20.4
Immune system disorders	20.0
Respiratory, thoracic, and mediastinal disorders	19.8
Psychiatric disorders	19.0
Nervous system disorders	16.4

SOC, system organ class

- For comorbid conditions that are known to have a high prevalence in COPD patients (hypertension, ischemic heart disease, hypercholesterolemia, diabetes, anxiety and depression), applicable preferred terms were grouped to combined endpoints in order to evaluate their prevalence in the population (Table 5). At baseline 38.7% of the patients had hypertension, 15.6% had conditions suggestive of ischemic heart disease, 16.7% were affected by hypercholesterolemia and/or hyperlipidemia, 9.8% had diabetes mellitus, and 13.7% were suffering from anxiety and/or depression.

Table 5. *Nonrespiratory comorbid conditions (combined endpoints) with known high prevalence in COPD patients (MedDRA PTs, pooled HandiHaler® patients, N=15,375)*

Preferred term	Patients, %*
a) Ischemic heart disease	
Acute MI	0.22
Angina pectoris	3.30
Angina unstable	0.06
Arteriospasm coronary	0.01
Coronary artery disease	7.54
Coronary artery insufficiency	0.32
Coronary artery occlusion	0.03
Coronary artery stenosis	0.02
Coronary artery thrombosis	0.01
Ischaemic cardiomyopathy	0.40
MI	3.75
Myocardial ischaemia	2.82
Prinzmetal angina	0.01
Silent MI	0.04
b) Hypertension	
Essential hypertension	1.11
Hypertension	37.55
Malignant hypertension	0.01
c) Hypercholesterolemia and/or hyperlipidemia	
Hypercholesterolemia	9.49
Hyperlipidemia	7.19

Table 5. *(continued)*

Preferred term	Patients, %*
d) Diabetes mellitus	
Diabetes mellitus	4.81
Hyperglycaemia	0.34
Insulin-requiring type 2 diabetes mellitus	0.05
Type 1 diabetes mellitus	0.40
Type 2 diabetes mellitus	4.24
e) Anxiety and/or depression	
Acute stress disorder	0.01
Agitation	0.01
Agoraphobia	0.02
Anxiety	4.82
Anxiety disorder	0.17
Depressed mood	0.03
Depression	9.09
Generalized anxiety disorder	0.05
Major depression	0.11
Nervousness	0.25
Panic attack	0.19
Panic disorder	0.10
Panic disorder with agoraphobia	0.01
Panic reaction	0.07
Phobia	0.01
Posttraumatic stress disorder	0.57
Social phobia	0.01
Stress	0.10
Tension	0.02

*Percentage includes patients having more than one preferred term

MedRA, Medical Dictionary for Regulatory Activities; PT, preferred term; MI, myocardial infarction

Conclusions

- Comorbid conditions commonly reported in epidemiological studies of COPD were also observed among the pooled tiotropium HandiHaler® clinical trial patient population.
- With the exception of hypercholesterolemia and/or hyperlipidemia, the percentages of patients with these comorbid conditions in the pooled clinical trials were similar or close to those observed in the epidemiological studies: hypertension (39% versus 40-55%), ischemic heart disease (16% versus 10-20%), diabetes (10% versus 13-25%), anxiety and/or depression (14% versus 8-39%), hypercholesterolemia and/or hyperlipidemia (17% versus 35-52%).[4-6]
- The pooled tiotropium HandiHaler® clinical trial patient population appears to be fairly representative of the general COPD patient population in terms of comorbid conditions.

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