Eur Respir J 2007; 30: 898–906
DOI: 10.1183/09031936.00104606

Premature discontinuation of patients: a potential bias in COPD clinical trials

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ABSTRACT: Premature discontinuation from clinical trials may bias results against effective therapies.

In the present study mortality rates were retrospectively reviewed in a 6-month, randomised, placebo-controlled trial in which tiotropium 18 μg daily was shown to decrease chronic obstructive pulmonary disease exacerbations. Patients participated for 6 months even if trial medication was prematurely discontinued. Exposure-adjusted incidence rates (IRs) were calculated for randomisation–end trial, randomisation–end trial drug (0–ED) and end trial drug–end trial (ED–ET).

Of 1,829 patients (forced expiratory volume in one second 1.04 L (36% predicted), mean age 68 yrs, 99% male), 16% tiotropium and 27% placebo patients prematurely stopped trial medication. The number of fatal events for the entire cohort was: 62 all cause, including 16 cardiac and 16 lower respiratory. IRs for fatal events per 100 patient-yrs were higher in the discontinued period: 1.9 (0–ED) *versus* 23.0 (ED–ET) in the tiotropium group and 1.8 *versus* 19.0 in the placebo group. Respective IRs for fatal cardiac events were 0.7 *versus* 2.8 (tiotropium) and 0.5 *versus* 6.2 (placebo); for fatal lower respiratory events were 0.7 *versus* 2.8 (tiotropium) and 0.8 *versus* 5.4 (placebo). Rate ratios (tiotropium/placebo) for fatal events were lower in the discontinued period: 1.4 *versus* 0.5 for cardiac and 0.9 *versus* 0.5 for lower respiratory.

Higher incidence rates of fatal events occurred following premature discontinuation of study medication. Incomplete information from rate ratios occurs as a result of failure to consider outcomes of patients who discontinue early from clinical trials.

KEYWORDS: Adverse events, bronchodilators, chronic obstructive pulmonary disease, clinical trials, discontinuation, tiotropium

Randomised, double-blind, controlled clinical trials are the cornerstone of development for pharmaceutical products and devices designed to improve the health of patients afflicted with acute and chronic diseases. However, there are many trial design issues that, when not adequately considered, can lead to unwanted biases.

A potential bias in clinical trials that has not received sufficient consideration is the differential discontinuation rate that may be seen when a highly active compound is compared with no treatment or with a significantly inferior compound. If the effectiveness of a drug cannot be perceived by the patient (*e.g.* an improvement in a blood test, such as low-density lipoprotein cholesterol) then the degree of benefit of the drug has no influence on a patient's decision to continue or discontinue a clinical trial. However, when the outcome is an important symptom for which patients have cognitive and emotional perceptions then the influence may be profound. An analogy may be drawn to pain studies. If the study is of short duration, such as a few hours or days, the patient may tolerate the discomfort for the study duration. However, over many weeks or months, such a patient may decide that their altruistic reason for participating in a clinical trial has gone beyond an acceptable threshold. A patient perceiving no benefit, yet suffering from continuous pain, may decide to withdraw from a study. If there is a differential discontinuation rate due to such a phenomenon, the conditions exist where the patients who continue in the trial and are receiving the inferior treatment would, on average, be less severely afflicted than patients who are receiving the superior treatment.

Other factors can also affect discontinuation and must be considered when examining this potential bias in the differential discontinuation rate. Patients and healthcare providers may choose to

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Received:
August 09 2006
Accepted after revision:
July 27 2007

STATEMENT OF INTEREST
A statement of interest for S. Kesten can be found at www.erj.ersjournals.com/misc/statements.shtml

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

participate in a clinical trial due to altruism or the hope of receiving an active drug that may not otherwise be available [1]. However, once in the trial, the patient or their healthcare provider may choose at any time to discontinue participation.

Tiotropium is the first once-daily inhaled medication for the treatment of chronic obstructive pulmonary disease (COPD). Clinical trials of tiotropium 18 μg once daily have consistently demonstrated benefits in lung function, dyspnoea, exercise tolerance, health-related quality of life and exacerbations [2–8]. NIEWOEHNER *et al.* [8] previously reported on a 6-month, randomised, double-blind, placebo-controlled clinical trial assessing the effects of tiotropium 18 μg once daily on exacerbations of COPD. The trial was conducted in the Veterans Affairs (VA) setting in the USA and demonstrated that tiotropium can reduce COPD exacerbations and associated hospitalisations. The trial was conducted using intention-to-treat principles in which patients were requested to complete follow-up for the full 6 months even if there was premature discontinuation of trial medication. The present authors therefore used the opportunity provided to examine how premature discontinuation can influence outcomes such as serious adverse event (SAE) and fatal adverse event.

METHODS

The methods have been described in the original publication [8] and are briefly summarised in the following sections.

Study design

A parallel-group, double-blind, randomised design was used to study exacerbations of COPD over a 6-month period in COPD patients (trial 205.266). Patients received tiotropium 18 μg once daily or matching placebo capsules delivered *via* a HandiHaler® (Boehringer Ingelheim International GmbH, Ingelheim, Germany) dry powder inhalation device in a 1:1 randomisation. All patients were receiving care in the VA medical system in the USA and were permitted to continue all previously prescribed respiratory medications other than inhaled anticholinergics. The proportion of patients with at least one exacerbation of COPD and the proportion of patients with at least one hospitalisation due to an exacerbation during the 6-month trial period represented the co-primary outcomes. The protocol was approved by local institutional review boards and all patients provided written, informed consent.

Study participants

Inclusion criteria included: a clinical diagnosis of COPD; age $\geqslant$40 yrs; a smoking history of $\geqslant$10 pack-yrs; and a forced expiratory volume in one second (FEV_1) $\leqslant$60% predicted and $\leqslant$70% of the forced vital capacity (FVC) [9, 10]. Exclusion criteria included: asthma; an exacerbation of COPD in the preceding month; myocardial infarction within the prior 6 months; serious cardiac arrhythmia or hospitalisation for heart failure within the previous year; known moderate-to-severe renal impairment; moderate-to-severe symptomatic prostatic hypertrophy or bladder-neck obstruction; and narrow-angle glaucoma.

Procedures

Qualified patients meeting inclusion and exclusion criteria were randomised following a screening visit. Visits were scheduled at 3 and 6 months following randomisation. Telephone contacts occurred monthly between clinic visits. Drug compliance was assessed through counts of returned capsules and patients were provided with diary cards to record drug use. Spirometry was conducted before and 90 min after study drug administration at baseline and at 3 and 6 months [11]. As per intention-to-treat principles, patients were requested to attend all study visits and provide medical information, even if study drug was discontinued prior to 6 months.

Exacerbations of COPD

According to the protocol and the published report, an exacerbation of COPD was defined as: ''a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnoea, or chest tightness with a duration of $\geqslant$3 days requiring treatment with antibiotics and/or systemic steroids and/or hospital admission'' [8].

Hospitalisations were confirmed using available medical records. Exacerbations of COPD were reported on an exacerbation-specific case report form. Exacerbation events considered serious, such as hospitalisations (for definition of serious see Adverse event reporting), were also reported on an SAE case report form. Data from both case report form sources were reconciled to ensure accuracy and consistency.

Adverse event reporting

All SAEs were reported by the clinical sites to Boehringer Ingelheim GmbH (Ingelheim, Germany) from the time of informed consent to the completion of the trial. Adverse events were defined as any untoward medical occurrence during the trial. An SAE was defined as any untoward medical occurrence during the trial (regardless of a judged relationship to active or placebo capsules) that: resulted in death; was immediately life-threatening; resulted in persistent or significant disability; required or prolonged a hospitalisation; or was deemed serious for any other reason representing a significant hazard that was comparable to the aforementioned criteria. SAEs were documented on case report forms. SAEs were recorded regardless of whether or not the site considered there to be a relationship to active treatment or placebo capsules. For SAEs that were fatal, the start date was recorded as the start of the event that became fatal and not necessarily the date of death. Nonserious adverse events were not systematically collected. The adverse event terms reported by the investigational sites were coded according to the standard medical coding dictionary [12] while the trial remained blinded. Modifications to the standard coding conventions (pre-specified prior to trial initiation) included dividing the respiratory system into upper, lower and other, as well as combining similar terminology for events of interest, such as COPD exacerbations.

Data analyses

A full description of the data analysis has been provided by NIEWOEHNER *et al.* [8]. Data were analysed from all patient contacts from the time of inhalation of the first dose of study drug to trial completion.

For adverse events, incidence rates (IRs) were calculated as the number of patients with an event divided by the person-yrs at risk [13]. Patients contributed person-time (calculated as

person-yrs) during the time they remained in the study until 30 days following the last dose of study medication or until they experienced the adverse event being assessed. Patients could contribute to multiple events but each event was analysed separately. If a patient was reported to have more than one occurrence of an identical event, only the time to the first event was utilised.

In the analysis examining the influence of premature discontinuations on adverse events, the analysis of adverse events included the number of patients experiencing the event, the calculated study drug exposure specific for the event, the IR (per 100 patient-yrs) and the rate ratio (RR; tiotropium/placebo) along with the associated 95% confidence intervals (CI). The calculated exposure represents the sum of the time of each patient in the specified time period.

IR in the tiotropium group divided by IR in the placebo group defined RR. The Mantel-Haenszel RR estimator was utilised for this analysis and 95% CI were determined for each event to determine the precision of the estimate [13].

IRs and RRs were calculated for serious and fatal adverse events (total, cardiac and lower respiratory), as well as for COPD exacerbations in the tiotropium and placebo groups using the time-frames as follows. 1) Entire trial period (0–ET): all events occurring over the 6 months from randomisation to the end of the clinical trial. For patients who discontinued study drug prior to 6 months and completed the trial, this included events occurring from the last day of study drug to the end of the trial. 2) Time on treatment (0–ED): events occurring from randomisation until the last day of study drug. 3) Time off treatment (ED–ET): events occurring from the last day of study drug until the end of the clinical trial (*i.e.* events occurring in patients who prematurely discontinued). 4) Time on treatment plus 30 days (0–ED30): events occurring from randomisation until the last day of study drug plus 30 days. The 30-day period immediately following the end of study drug was examined to include any potential residual effects of the drug. According to the protocol, SAEs, including deaths, were assigned to a treatment group if they occurred within 30 days of the last dose of study medication. 5) Time off treatment starting 31 days after study drug (ED30–ET): events occurring from 31 days after the last dose of study drug to the end of the clinical trial (*i.e.* events occurring in patients who prematurely discontinued, which, according to protocol, are not the effect of the study drug).

Adverse event data were analysed for the cardiac and lower respiratory systems since, as expected in the present population, these were the most common adverse events. COPD exacerbations were analysed as this was the primary outcome of the trial.

RESULTS

A total of 1,829 patients were randomised, of which 914 received tiotropium and 915 received placebo. Information at the conclusion of the trial was obtained in ~90% of patients. From the tiotropium group, 75 (8.2%) patients withdrew from the trial and 74 (8.1%) patients prematurely discontinued trial drug but completed the trial. From the placebo group, 111 (12.1%) patients withdrew from the trial and 134 (14.6%) patients prematurely discontinued trial drug but completed the trial. In total, trial medication was prematurely stopped by 16.3% of tiotropium-treated patients and 26.7% of placebo patients ($p<0.0001$). The major reasons for either prematurely discontinuing trial drug or withdrawing from the trial were worsening of COPD and other adverse events.

Study population

The mean age of the population was 68 yrs and 99% were males (table 1) [8]. The mean FEV_1 was 1.04 L (36% pred) and FEV_1/FVC was 48% [8]. Demographic features and baseline respiratory medications were balanced between treatment groups [8]. The FEV_1 % pred in tiotropium patients who did not complete study medication but completed the trial was higher than the corresponding placebo group (35.4 *versus* 30.9%), suggesting that patients with the lowest lung function preferentially discontinued early in the placebo group. The baseline age, FEV_1 and respiratory medications for the patients who completed the trial, discontinued study drug and continued in the trial, and those who prematurely discontinued both study drug and the trial are listed in table 2. The proportion of patients receiving respiratory medications at any time (continuous, short-course or single dosing) during the trial period is displayed in table 3.

TABLE 1 Baseline characteristic of the tiotropium and placebo groups

	Tiotropium	Placebo
Subjects	914	915
Males	898 (98)	904 (99)
Age yrs	67.6±8.7	68.1±8.5
White ethnicity	847 (93)	823 (90)
Smoking status		
Current smoker	263 (29)	272 (30)
Pack-yr history	67.4±35.4	69.4±36.6
Duration of COPD yrs	12.2±10.4	11.9±10.5
Baseline spirometry		
FEV_1 L	1.04±0.40	1.04±0.40
FEV_1 % pred	35.6±12.6	35.6±12.6
FEV_1/FVC %	47.9±11.5	47.7±11.1
Medication for COPD		
Inhaled β-agonist		
Any	851 (93)	864 (94)
Nebulised	237 (26)	234 (26)
Long-acting	346 (38)	351 (38)
Ipratropium bromide		
Any	735 (80)	728 (80)
Nebulised	138 (15)	157 (17)
Corticosteroids		
Inhaled	559 (61)	531 (58)
Oral	94 (10)	97 (11)
Theophylline	141 (15)	118 (13)
Leukotriene antagonist	59 (6)	53 (6)
Home oxygen	259 (28)	272 (30)

Data are presented as n, n (%) or mean±SD. COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity. Data taken from [8].

TABLE 2 Baseline age, forced expiratory volume in one second (FEV_1) and respiratory medications according to treatment group and completion/discontinuation status

	Completed trial and study drug		Discontinued trial#		Discontinued study drug¶	
	Tiotropium	Placebo	Tiotropium	Placebo	Tiotropium	Placebo
Subjects n	762	670	78	111	71	134
Age yrs	68±9	68±9	67±9	67±9	69±8	70±9
FEV_1 L	1.05±0.40	1.07±0.39	0.96±0.42	1.02±0.40	0.99±0.40	0.89±0.39
FEV_1 % pred	36±12	37±12	33±13	35±12	35±15	31±13
Respiratory medication %+						
Anticholinergic	79	77	84	84	89	87
Long-acting β-agonist	39	38	28	34	39	45
Inhaled steroid	61	57	65	62	74	68
Theophylline	16	12	9	15	13	23
Oral steroid	10	9	9	8	14	23
Oxygen	25	25	31	30	31	40

Data are presented as mean±SD, unless otherwise stated. % pred: % predicted. #: incomplete follow-up after study drug discontinuation; ¶: followed for duration of trial after drug discontinuation; +: proportion of population.

Efficacy outcomes

As described by NIEWOEHNER *et al.* [8], the proportion of patients experiencing exacerbations of COPD was reduced in the tiotropium group ($p<0.05$), while the difference in hospitalisations approached statistical significance ($p=0.056$). There were significant reductions in the time to first exacerbation or hospitalisation along with reductions in the number of events [8].

Safety

The calculated study drug exposure was ~416.1 patient-yrs in the tiotropium arm and 380.0 patient-yrs in the placebo arm. A total of 344 patients reported at least one SAE (174 and 170 in the tiotropium and placebo groups, respectively). The SAEs were widely distributed among various organ systems, with the majority of events occurring at a low frequency (*i.e.* one or two patients with a specific event). A total of 62 patients died during the study.

SAEs

Exposure-adjusted IRs for any SAE and for cardiac and lower respiratory events are displayed in table 4. For any SAE, IRs appeared to be similar across groups during all time periods, except for an increase in the tiotropium group in ED30–ET.

For cardiac and respiratory adverse events, IR appeared lower in the tiotropium group relative to the placebo group during study drug treatment (0–ED and 0–ED30) and for 0–ET. There was approximately a two-fold increase in the IR of these events in the placebo group following premature discontinuation of study drug relative to the on-treatment period: 17.4 cardiac SAEs in ED–ET *versus* 8.8 in 0–ED; and 30.3 lower respiratory SAEs in 0–ED *versus* 18.7 in 0–ED. Similar results were seen relative to the corresponding period with tiotropium: 17.4 cardiac SAEs with placebo *versus* 7.9 with tiotropium in ED–ET; and 30.3 lower respiratory SAEs with placebo *versus* 17.4 with tiotropium in ED–ET. RRs (tiotropium/placebo) and 95%

TABLE 3 Respiratory medications used at any time during the trial period according to treatment group and completion/discontinuation status

	Completed trial and study drug		Discontinued trial#		Discontinued study drug¶	
	Tiotropium	Placebo	Tiotropium	Placebo	Tiotropium	Placebo
Subjects n	762	670	78	111	71	134
Respiratory medication %+						
Anticholinergic	5	6	24	32	73	86
Long-acting β-agonist	47	45	28	34	50	54
Inhaled steroid	61	57	45	51	72	75
Theophylline	17	14	5	10	22	15
Oral steroid	15	15	11	17	31	38
Oxygen	29	31	31	26	45	52

#: incomplete follow-up after study drug discontinuation; ¶: followed for duration of trial after drug discontinuation; +: proportion of population.

TABLE 4 Exposure-adjusted incidence rates (IR; per 100 patient-yrs) of total (any), cardiac and lower respiratory serious adverse events (SAEs) in the tiotropium and placebo group according to onset of event

Onset	Tiotropium[#]			Placebo[¶]			Risk ratio (95% CI) tiotropium/placebo
	n	Exposure	IR	n	Exposure	IR	
Any SAE							
0–ET	174	464	37.5	170	456	37.3	1.01 (0.82–1.24)
0–ED	146	387	37.8	129	355	36.3	1.04 (0.82–1.32)
ED–ET	28	77	36.3	41	101	40.6	0.89 (0.55–1.45)
0–ED30	162	449	36.1	156	428	37.3	0.97 (0.78–1.21)
ED30–ET	12	15	79.5	14	38	36.8	2.16 (1.00–4.67)
Cardiac SAE							
0–ET	38	512	7.4	54	495	10.9	0.68 (0.45–1.03)
0–ED	30	411	7.3	33	374	8.8	0.83 (0.51–1.36)
ED–ET	8	101	7.9	21	121	17.4	0.45 (0.20–1.03)
0–ED30	33	483	6.8	48	446	10.8	0.64 (0.41–0.99)
ED30–ET	5	29	17.3	6	49	12.2	1.42 (0.43–4.65)
Lower respiratory SAE							
0–ET	80	496	16.1	103	480	21.4	0.75 (0.56–1.01)
0-ED	64	4	15.8	69	368	18.7	0.85 (0.60–1.19)
ED–ET	16	92	17.4	34	112	30.3	0.58 (0.32–1.04)
0–ED30	72	474	15.2	90	437	20.6	0.74 (0.54–1.01)
ED30–ET	8	22	35.9	13	44	29.6	1.21 (0.50–2.93)

n: number of events; CI: confidence interval; 0–ET: entire trial period; 0–ED: time on treatment; ED–ET: time off treatment; 0–ED30: time on treatment plus 30 days; ED30–ET: time off treatment starting 31 days after study drug. [#]: n=914; [¶]: n=915.

CIs for all of the SAEs, and for cardiac and lower respiratory SAEs in the tiotropium and placebo group according to onset of event are displayed in figure 1. Examination of the data suggests that many of these events in the placebo group occur within a 30-day window of cessation of study drug.

Fatal events

Exposure-adjusted IRs for any fatal event and for fatal cardiac and lower respiratory events are displayed in table 5. For any fatal event, the IRs were >10-fold higher after premature cessation of study drug in both groups, with most of the difference occurring in the 30 days following cessation of study drug.

For cardiac and respiratory fatal events, the IR appeared similar in the tiotropium and control groups during the study drug treatment. However, IRs were lower with tiotropium for 0–ET. There was approximately a four-fold higher IR of these events in the tiotropium group following premature discontinuation of the study drug relative to the on-treatment period: 2.8 cardiac fatal SAEs in ED–ET *versus* 0.7 in 0–ED; and 2.8 lower respiratory fatal SAEs in ED–ET *versus* 0.7 in 0–ED.

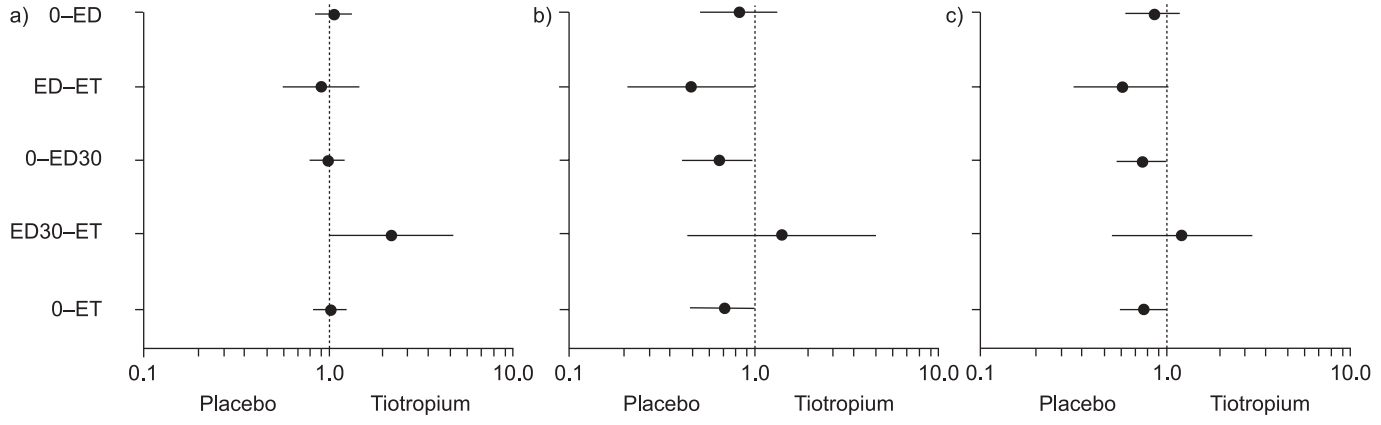

FIGURE 1. Rate ratios and 95% confidence intervals of a) total (any), b) cardiac and c) lower respiratory serious adverse events in the tiotropium and placebo group according to onset of event. 0–ED: time on treatment; ED–ET: time off treatment; 0–ED30: time on treatment plus 30 days; ED30–ET: time off treatment starting 31 days after study drug; 0–ET: entire trial period.

TABLE 5 Exposure-adjusted incidence rates (IR; per 100 patient-yrs) of total (any), cardiac and lower respiratory fatal events in the tiotropium and placebo group according to onset of event

Onset	Tiotropium#			Placebo¶			Risk ratio (95% CI) tiotropium/placebo
	n	Exposure	IR	n	Exposure	IR	
Any fatal event							
0–ET	31	516	6.0	31	506	6.1	0.98 (0.60, 1.61)
0–ED	8	416	1.9	7	380	1.8	1.04 (0.38, 2.88)
ED–ET	23	100	23.0	24	126	19.0	1.21 (0.68, 2.14)
0–ED30	22	490	4.5	19	454	4.2	1.07 (0.58, 1.98)
ED30–ET	9	26	34	12	52	23.1	1.47 (0.62, 3.49)
Cardiac fatal event							
0–ET	6	523	1.2	10	509	2.0	0.58 (0.21, 1.61)
0–ED	3	416	0.7	2	380	0.5	1.37 (0.23, 8.20)
ED–ET	3	107	2.8	8	129	6.2	0.45 (0.12, 1.70)
0–ED30	3	491	0.6	6	455	1.3	0.46 (0.12, 1.85)
ED30–ET	3	32	9.4	4	54	7.4	1.26 (0.28, 5.65)
Lower respiratory fatal event							
0–ET	6	522	1.2	10	509	2.0	0.59 (0.21, 1.61)
0–ED	3	416	0.7	3	380	0.8	0.91 (0.18, 4.52)
ED–ET	3	106	2.8	7	129	5.4	0.52 (0.14, 2.02)
0–ED30	3	491	0.6	7	455	1.5	0.40 (0.10, 1.54)
ED30–ET	3	31	9.7	3	54	5.5	1.75 (0.36, 8.71)

n: number of events; CI: confidence interval; 0–ET: entire trial period; 0–ED: time on treatment; ED–ET: time off treatment; 0–ED30: time on treatment plus 30 days; ED30–ET: time off treatment starting 31 days after study drug. #: n=914; ¶: n=915.

This appeared to be more prominent in the placebo group, with an approximately seven-fold increase relative to the on-treatment period: 6.2 cardiac fatal SAEs in ED–ET *versus* 0.5 in 0–ED; and 5.4 lower respiratory fatal SAEs in ED–ET *versus* 0.8 in 0–ED. Results were also higher relative to the corresponding period with tiotropium: 6.2 cardiac fatal SAEs with placebo *versus* 2.8 with tiotropium in ED–ET; and 5.4 lower respiratory fatal SAEs with placebo *versus* 2.8 with tiotropium in ED–ET. Examination of the data suggests that many of these events in the placebo group occur within a 30-day window of cessation of study drug. The corresponding RRs (tiotropium/placebo) and 95% CIs are displayed in figure 2.

COPD exacerbations

Exposure-adjusted IRs for serious and fatal COPD exacerbations are displayed in table 6. For serious exacerbations, IRs were higher by approximately two-fold in the placebo group after premature cessation of study drug (22.1 in ED–ET *versus* 12.4 in 0–ED), whereas it appeared similar in the tiotropium group (9.2 in ED–ET *versus* 8.8 in 0–ED). However, in the tiotropium group, the rate was higher after 30 days following cessation of study drug (26.9 in ED30–ET *versus* 7.9 in 0–ED30). The RR between the two groups (tiotropium/placebo) was lower with tiotropium, with RR being lowest in the period following cessation of study drug (fig. 3).

There were five fatal COPD exacerbations in the control group and none in the tiotropium group. However, four out of five events appeared in the period following cessation of study drug, with three occurring in the 30-day period immediately after cessation of study drug. RRs could not be calculated given the absence of events in the tiotropium group.

DISCUSSION

The completion of a recent tiotropium clinical trial using an intention-to-treat design provided a unique opportunity to evaluate potential biases induced by study designs in standard COPD clinical trials in which patient participation ends upon termination of the intervention. The present study was a large, randomised, double-blind, placebo-controlled clinical trial of 6 months of duration in which the primary outcome was COPD exacerbations. Patients were permitted to continue use of any previously prescribed respiratory medication other than inhaled anticholinergics. Information at the conclusion of the trial was obtained in ~90% of patients. However, premature discontinuation of trial drug occurred in 14.6% of the control group and 8.1% of the tiotropium group who continued to be followed for the complete 6-month study duration. Exposure-adjusted IRs of serious and fatal adverse events were retrospectively reviewed and a differential effect of the treatment arms dependent of the trial period was observed. For the most common and most relevant events in the present population (*i.e.* cardiac and lower respiratory events), there was a higher incidence of events in the post-treatment period. Furthermore, there was a higher risk of experiencing such events in the post-treatment period in the control group relative to the tiotropium group. This differential was higher than that observed in the on-treatment period and was most prominent in the immediate 30 days following discontinuation of study medication,

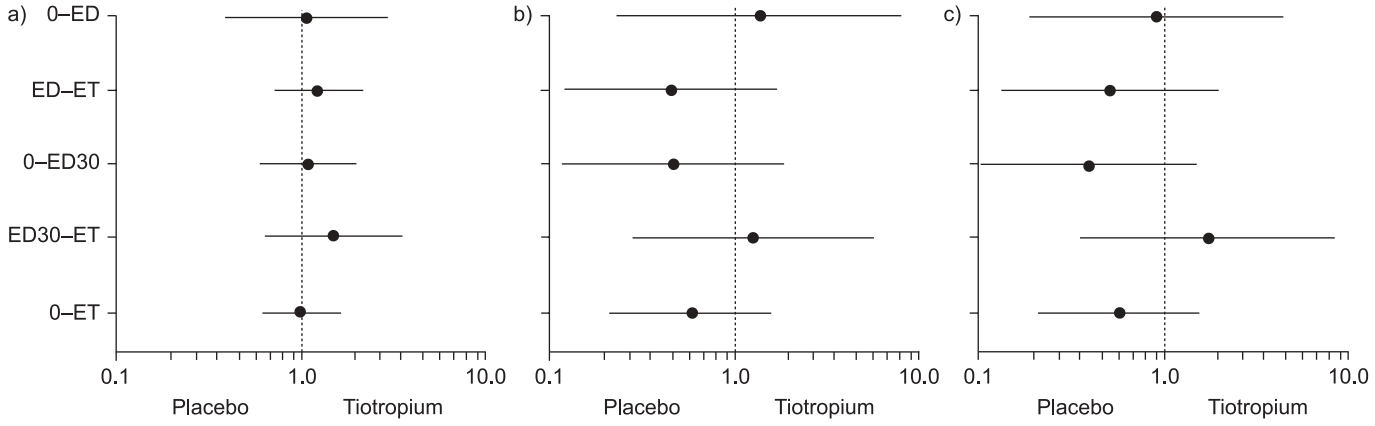

FIGURE 2. Rate ratios and 95% confidence intervals of a) total (any), b) cardiac and c) lower respiratory fatal adverse events in the tiotropium and placebo group according to onset of event. 0–ED: time on treatment; ED–ET: time off treatment; 0–ED30: time on treatment plus 30 days; ED30–ET: time off treatment starting 31 days after study drug; 0–ET: entire trial period.

highlighting the potential impact that such data can have on the interpretation of results from clinical trials.

Careful consideration of the design and analyses of clinical trials is mandatory to attain outcomes that can be interpreted in the most unambiguous manner. There are certain types of clinical outcomes that, by their nature, minimise potential complexities in interpretation. Trials of acute bronchodilators often involve direct observation for the entire treatment period and achievement of complete follow-up with minimal biases introduced can be reasonably expected [14, 15]. The study of chronic diseases such as COPD, which often have complex outcomes, becomes much more problematic. In studies extending over months or years, the patient resides in an uncontrolled setting (*i.e.* their home) and is subject to social and occupational environments that result in exposure to a host of uncontrolled influences. Nevertheless, these factors should be randomly and equally distributed between study groups with large enough sample sizes. Yet, when there is a clear differential in the effectiveness of one treatment arm over time, other unanticipated biases may occur. These biases could influence a primary outcome, such as lung function, symptom improvement, worsening of the underlying disease or mortality.

How might such a bias occur? In the case of a highly effective drug matched against an ineffective intervention, this bias can occur when patients in the active group are more likely to complete the trial than those in the inactive group [3–5]. This can be expected when an outcome is of importance to the patient. In the case of COPD, this could include improvements in dyspnoea and exercise tolerance and a reduction in exacerbations [16]. The disease is also characterised by periodic acute and sub-acute worsenings (*i.e.* exacerbations).

TABLE 6 Exposure-adjusted incidence rates (IR; per 100 patient-yrs) of serious and fatal exacerbations of chronic obstructive pulmonary disease (COPD) in the tiotropium and placebo group according to onset of event

Onset	Tiotropium[#]			Placebo[¶]			Risk ratio (95% CI) tiotropium/placebo
	n	Exposure	IR	n	Exposure	IR	
Serious COPD exacerbation							
0–ET	45	508	8.9	72	489	14.7	0.60 (0.41–0.87)
0–ED	36	410	8.8	46	371	12.4	0.71 (0.46–1.10)
ED–ET	9	98	9.2	26	117	22.1	0.42 (0.19–0.89)
0–ED30	38	482	7.9	61	442	13.8	0.57 (0.38–0.86)
ED30–ET	7	26	26.9	11	47	23.5	1.15 (0.45–2.96)
Fatal COPD exacerbation							
0–ET	0	523	0	5	510	1.0	N/A
0–ED	0	416	0	1	380	0.3	N/A
ED–ET	0	107	0	4	130	3.1	N/A
0–ED30	0	491	0	3	455	0.7	N/A
ED30–ET	0	32	0	2	55	3.7	N/A

n: number of events; CI: confidence interval; 0–ET: randomisation to end of trial (entire trial period); 0–ED: randomisation to end of drug (time on treatment); ED–ET: end of drug to end of trial (time off treatment); 0–ED30: randomisation to end of drug (time on treatment) plus 30 days; ED30–ET: from 31 days after end of drug to end of trial; N/A: no patients in the tiotropium group had a fatal COPD exacerbation. [#]: n=914; [¶]: 915.

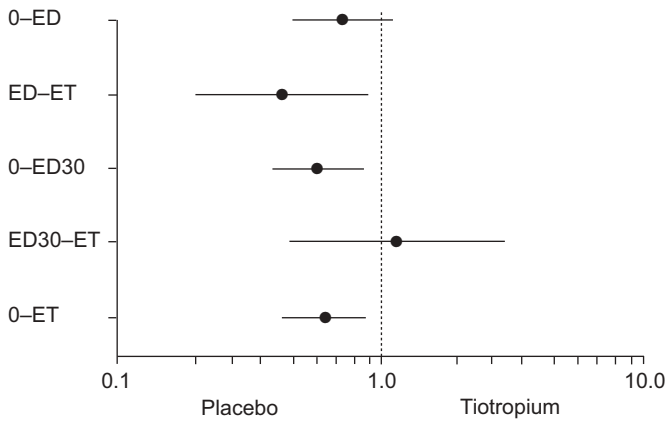

FIGURE 3. Rate ratios and 95% confidence intervals of chronic obstructive pulmonary disease exacerbations reported as serious adverse events in the tiotropium and placebo group according to onset of event. 0–ED: time on treatment; ED–ET: time off treatment; 0–ED30: time on treatment plus 30 days; ED30–ET: time off treatment starting 31 days after study drug; 0–ET: entire trial period.

Although patients enter for altruistic reasons, there is also hope of receiving an active drug that could improve their underlying condition [1]. Failure to meet the expectation for improvement along with the continued limitations invoked by COPD may lead to premature discontinuation, particularly in longer term trials. For example, in a 3-yr trial of inhaled steroids in COPD, discontinuations exceeded 40% [17]. Furthermore, patients could experience sub-acute or acute worsening of the disease, which may lead to the investigator or the patient deciding that participation should be terminated prematurely. While such an event should be recorded as worsening of underlying COPD or a COPD exacerbation, it may simply be viewed as withdrawing consent or termination for other reasons. The situation may further be exaggerated in the case of a marketed product, where the patient and healthcare provider know that an active and efficacious medication may be purchased.

In the case of tiotropium, multiple clinical trials indicate that improvements in dyspnoea, exercise tolerance, health-related quality of life and exacerbations can reasonably be expected [3–8]. However, in previous clinical trials with tiotropium of $\geqslant$6 months of duration, patient participation ended with the last day of study drug (either prematurely or because they completed the full course of study drug treatment) [3–5]. While investigators were asked to report any SAEs in the 30 days following the last day of study drug, follow-up visits were not part of the trial protocols. In each of these trials, the tiotropium-treated group was associated with a lower frequency of premature discontinuations [3–5]. The present study is the first reported tiotropium trial in which follow-up information in patients who prematurely discontinued study medication was systematically collected [8].

There were several observations worthy of further discussion. First, it is hypothesised that patients who discontinue early, often do so because they have more severe underlying disease, are more predisposed to clinically important worsening of the condition and are at higher risk of dying. This is indeed the case based on the analysis. Examination of the control group indicated multifold increases in the IR of death, serious respiratory and serious cardiac events. Secondly, if the hypothesis is true, it may be expected that such events would preferentially surface shortly after prematurely discontinuing treatment, thereby suggesting an association. Again, data in the control group support this conjecture. Finally, it is surmised that this finding would preferentially be observed in the control group in the case of a comparison to a highly active compound. This observation is particularly notable with regard to one of the more important clinical outcomes and, for this trial, the primary outcome. Serious lower respiratory events including exacerbations occurred with a lower IR in the tiotropium group during study drug treatment, but this difference was exaggerated during the period following early discontinuation. Furthermore, there was no difference in mortality due to lower respiratory events during the treatment period but a difference appeared during the post-treatment period, which was most prominent during the initial 30 days. Indeed, for fatal exacerbations, there was one case during treatment in the control group *versus* none in the tiotropium group; however, at the end of the trial, there was five in the control group *versus* zero with tiotropium.

The implications of these observations are highly significant. Results from clinical trials with highly efficacious benefits for important clinical outcomes may be underestimated due to differential discontinuation rates (*i.e.* the ''healthier survivor'' effect) in the control group if follow-up data is not collected on patients who prematurely discontinue study medication. In the worst case, imbalances may be observed in important adverse events, such as fatal events, in the disease under study, which are unfavourable for the active treatment group. In other words, there may be a greater number of deaths in the active arm of a highly effective intervention due to early discontinuation of the most severely afflicted patients in the control group who are destined to die in the short term. Inaccurate conclusions could be drawn that could diminish or eliminate the use of effective treatments in serious chronic diseases.

CALVERLEY *et al.* [18] reported the determinants of patient withdrawal from the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study. ISOLDE was a double-blind, placebo-controlled, randomised clinical trial evaluating the effect of inhaled steroids on the rate of decline of FEV_1 [17]. More patients in the placebo group withdrew prematurely due to frequent courses of oral corticosteroids, which was most prominent in patients with FEV_1 <50% pred normal value at study entry [18]. However, this analysis was based only on data obtained while patients received study drug, as patients who stopped study drug were withdrawn from the trial. A subsequent publication of follow-up of causes of death in the ISOLDE trial has appeared in abstract form only [19]. Deaths were checked against centralised records in England and Scotland (both UK). The crude incidence of death was higher in patients withdrawn from the study.

The present tiotropium study has the advantage of pre-specification of collection of follow-up data in patients who prematurely discontinued trial medication. While data was not obtained in ~10% of discontinued patients, the availability of follow-up data in 90% can be considered high in light of the disease and duration of the trial. A potential limitation in the

present study is that the analysis is retrospective. It has been noted that there are occasions when the last day of study drug was recorded as the day prior to an adverse event and, therefore, the event would be considered to have occurred within the prematurely discontinued period. Retrospectively, it is difficult to be certain whether such events should be included in the data for the active drug treatment period. A sensitivity analysis suggests that the impact of this is small and does not alter the conclusions of the present study. A strength of the study is that the trial was conducted entirely in the VA medical system. The VA system is a relatively closed system and has electronic medical records, which increased the reliability of the data and decreased the likelihood of missing information. Patients tend to stay within the VA system, although they have the option of seeking healthcare outside. In addition, hospital discharge records were aggressively sought and reviewed, while the study team remained blinded to treatment allocation.

In summary, in a large, randomised, double-blind, controlled trial of 6 months of duration examining exacerbations of chronic obstructive pulmonary disease, important clinical differences in serious adverse events, including fatal events, were observed depending on the time following premature discontinuation of study medication. *A priori* inclusion in the protocol of collection of follow-up data for discontinued patients led to the observation of an overall higher incidence of cardiac and respiratory serious events during the post-treatment period, as well as the observation of differences between treatment groups in the incidence of these events in favour of the active drug (tiotropium) during the post-treatment period. The post-treatment period data suggest that the benefits of tiotropium would be underestimated without inclusion of the data. These observations suggest that all long-term trials in chronic obstructive pulmonary disease should consider the impact of early discontinuations of trial medication when the active arm is anticipated to have significant clinical benefits. While complete follow-up of patients who stop study drug is desirable, the challenges involved in trying to obtain and interpret follow-up data should be considered when designing clinical trials.

ACKNOWLEDGEMENTS

The authors wish to gratefully acknowledge the editorial support of T. Keyser (Boehringer Ingelheim, Inc., Ridgefield, CT, USA) and the statistical support of N. Spier (NAS Technical Services, Inc., Danbury, CT, USA).

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