Premature discontinuation during the UPLIFT study

Marc Decramer [a,*], **Geert Molenberghs** [a,b], **Dacheng Liu** [d], **Bartolome Celli** [c], **Steven Kesten** [d], **Theodore Lystig** [d], **Donald P. Tashkin** [e], on behalf of the UPLIFT investigators

[a] University of Leuven, Belgium
[b] University of Hasselt, Diepenbeek, Belgium
[c] Brigham and Women's Hospital, Harvard Medical School, Boston, USA
[d] Boehringer Ingelheim Pharmaceuticals, Ridgefield, USA
[e] David Geffen School of Medicine UCLA, Los Angeles, USA

Summary

Rationale: Placebo-controlled clinical trials on COPD are characterized by premature discontinuation. At present, no clear insight into this phenomenon is available.
Objective: To obtain better insight into the phenomenon of premature discontinuation.
Methods: We analyzed the pattern of discontinuation in the UPLIFT-trial.
Measurements and main results: Premature discontinuation was substantial and greater in the placebo than in the tiotropium group (45 vs. 37%, $p < 0.001$). Patients discontinuing were characterized by more severe COPD ($p < 0.0001$), greater number of pack years ($p < 0.002$), smaller pre-bronchodilator and post-bronchodilator FEV_1 ($p < 0.0001$ for both), and worse SGRQ scores ($p < 0.0001$). Rates of decline of FEV_1 and SGRQ were greater in non-completers ($p < 0.0001$ for both). The latter differences increased over time indicating that the evolution of variables in time was related to trial completion. The risks of exacerbations and hospitalizations were greater in non-completers. In logistic regression analysis BMI, post-bronchodilator FEV_1, male gender and treatment with tiotropium were positively related to trial completion, whereas age, worse SGRQ, female gender, current smoking and assignment to the placebo group were negatively related.
Conclusion: Assignment to the control group is related to premature discontinuation. Discontinuation was important and selective in this large trial. Pulmonary function, health-related quality of life and smoking are the most important other variables related to discontinuation. The evolution of variables during the trial is also related to discontinuation. Complete follow-up of discontinued patients may provide better insight into the efficacy of medication in future trials.
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* Corresponding author. Respiratory Division, University Hospital, University of Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16 346807.
E-mail address: Marc.Decramer@uzleuven.be (M. Decramer).

Introduction

During the last decade several large trials examining the effects of pharmacotherapy on the progression of chronic obstructive pulmonary disease, COPD, have been performed.[1–8] It has now been clearly demonstrated that in all of these trials premature discontinuation rates were very high ranging from 27% to 53% in the longer term studies.[9] Moreover, it has become abundantly clear that discontinuation does not occur randomly without pattern. To begin with, in virtually all of these trials drop-out rates were substantially greater in the placebo group than in the active treatment group, ranging from 29 to 53% and from 26 to 43%, respectively. But more importantly in breaking the "missing completely at random" assumption, patients dropped-out faster from the placebo group and the patients discontinuing from the placebo group were generally worse than those discontinuing from the active treatment group, both at baseline and during the study.

In recent years, it has been recognized that this premature discontinuation impacts the statistical analysis and hence, the observed treatment effects. This phenomenon underscores the need for an intention-to-treat (ITT)-analysis which may be viewed as a superior approach compared to commonly used analyses, such as complete case (CC) analysis, per protocol analysis or last observation carried forward (LOCF). Standard likelihood methods and Bayesian inferences are valid under "missingness at random" (MAR), which refers to the situation under which missingness is allowed to depend on observed outcomes and covariates but not further on unobserved outcomes. Note that MAR contains "missingness completely at random" (MCAR) as a special case. MCAR implies that missingness can depend on covariates but not on outcomes, whether observed or not. As such, it is a stronger condition than MAR. MCAR is required for CC to hold. Even under MCAR, is LOCF not necessarily valid, as it requires a different and highly unrealistic set of conditions to hold (such as the lack of evolution after drop-out). All methods mentioned are not valid under the most general missing data mechanism, "missingness not at random" (MNAR), which refers to the fact that, in addition to covariates and observed outcomes, also unobserved outcomes influence the probability of missingness.[10]

Suissa analyzed the effects of selective discontinuation on the rate of decline of forced expiratory volume in 1 s (FEV$_1$), one of the frequently used outcomes of these studies[11] in the Canadian Optimal trial.[12] In this trial, patients with the lowest FEV$_1$ had the lowest decline and conversely, patients with the highest FEV$_1$ had the highest rate of decline. Hence, excluding a large fraction of the worst patients as occurs in the placebo group could lead to an overestimation of the rate of decline and conversely, excluding a smaller fraction of these patients as occurs in the active treatment group might lead to less of an overestimation of the rate of decline. As a consequence, the end-result could appear as if a treatment effect would be present on rate of decline of FEV$_1$,[8] whereas in reality there is none. Similar concepts may apply to mortality and exacerbations, which constitute other important outcomes in COPD studies.[11–16] Along these lines, evidence is present that mortality rate is indeed high in discontinued patients.[6]

Little information is presently available on the characteristics of discontinued patients, the mechanisms governing discontinuation, and models predicting discontinuation from COPD trials. Such information can be critically important and needs to be considered when preparing an analysis plan and when interpreting observed treatments effects. The present manuscript is a secondary analysis from the recently published UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium)-trial. Its purpose is: 1) to describe the pattern of drop-out as a function of time and duration of the trial in a large 4 year trial; 2) to compare the baseline and in trial characteristics of completers and non-completers; 3) to construct a model predicting premature discontinuation on the basis of the functional characteristics observed at baseline and during the trial.

Materials and methods

Design

The details of the study design of the UPLIFT-trial have been reported previously.[7,17,18] Briefly, the study was a 4-year, randomized, double-blind, placebo-controlled, parallel-group study involving patients with moderate-to-very severe COPD. The two co-primary endpoints were the yearly rate of decline in pre-bronchodilator and post-bronchodilator FEV$_1$. Secondary endpoints were lung function at each visit, health status measured with the St. George's Respiratory Questionnaire (SGRQ), exacerbations and exacerbation-related hospitalizations, and mortality from all causes and from lower respiratory conditions. More details are provided in the on-line repository.

Patients received either 18 μg of tiotropium or a matching placebo, once daily, delivered via the Handi-Haler® (Boehringer-Ingelheim, Germany). All concomitant respiratory medications, except inhaled anticholinergics, were allowed during the trial. Details on patient recruitment and inclusion/exclusion criteria have been reported previously.[7,17,18] Briefly, 5993 patients were randomized to either tiotropium ($n = 2987$) or to placebo ($n = 3006$).

Measurements

Spirometry was performed according to the American Thoracic Society guidelines at randomization, at 1-month and then every 6 months until the end of the study period.[19] The details of this examination have been published previously.[7,17]

Health-related quality of life was measured using the St. George's Respiratory Questionnaire, which was administered prior to spirometry. Exacerbations were defined as an increase or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting for at least three days and requiring treatment with an antibiotic, systemic steroid or both.

Safety

Adverse events were recorded at each clinic visit. Data regarding vital status were requested for all patients who

prematurely discontinued study drug prior to 4 years from the first day of study drug administration. Mortality analysis was performed both for on-treatment mortality and on-treatment mortality + vital status data of discontinued patients at the end of the treatment period (day 1440) and at the end of the 30 days follow-up period after treatment (day 1470).[7,18]

Statistical analysis

Decline of pulmonary function vs. time was analyzed with random coefficient regression in which the FEV_1 changed linearly after 30 days for each patient, intercepts and slopes were random and the treatment effect was fixed. The same model was used for SGRQ decline vs. time (from 6 months until completion of the study). All patients who underwent randomization and received study drug and who had at least three post-randomization measurements of pulmonary function (at least two for SGRQ) were used in the analysis.

Cox regression was used to calculate hazard ratios. Kaplan–Meier curves of the probability of no exacerbation and consequent hospitalization were constructed.[20] The number of events and event days were compared between the study groups with relative risks through the use of Poisson regression with correction for overdispersion.[20]

A logistic regression model was constructed to predict trial completion.[20] Variables were selected stepwise from: age, gender, race, height, weight, body-mass index (BMI), smoking status, baseline pre-bronchodilator FEV_1, post-bronchodilator FEV_1, region, baseline use of long-acting beta-agonists (LABA), use of inhaled corticosteroids (ICS) and SGRQ total score. Pack years was not entered in the model because this variable is dependent on age. Variables with p-values <0.05 were retained in the final model. Completion was defined as completion of 45 months of treatment and no discontinuation due to adverse event after 45 months.

Analyses were performed with SAS software, version 8.2 (SAS Institute, Cary, North-Carolina). All reported p-values are two-sided and not corrected for multiple testing.

Role of the funding source

The study was supported by Boehringer-Ingelheim and Pfizer. The design of the trial, monitoring of the conduct, review and interpretation of the data, approval of the statistical analyses, writing of the manuscript, and decision to publish the manuscript involved a joint advisory committee composed of four academics (three investigators, MD, BC, DT and a statistician, Steph Senn), three researchers employed by Boehringer-Ingelheim (SK, Deborah Burkhart, Shailendra Menjoge) and a representative of Pfizer (Sunil Mehra). DL performed the statistical analysis of the present data as an employee of Boehringer-Ingelheim. GM was involved in the present analysis and its interpretation, because of his expertise in statistics with missing data. The first draft of the paper was written by an academic investigator (MD), and the final content of the manuscript was developed in
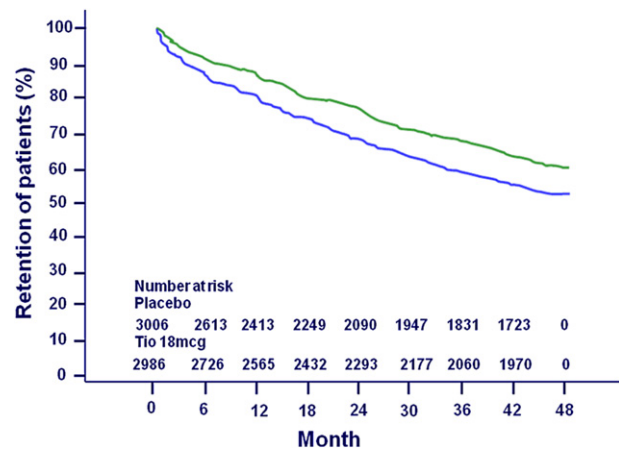

Figure 1 Probability of completion of study drug vs. duration of the study. Tiotropium, (——), Control, (——) (modified from[7]).

collaboration by all authors. All authors had full access to the data and guarantee the accuracy and completeness of the data and the analyses. The final responsibility for the decision to submit the manuscript was borne by the first author (MD).

Results

Pattern of discontinuation as a function of time and duration of the trial

In total, 5993 patients were randomized, 2987 and 3006 in the tiotropium and placebo group, respectively. A total of 1100[f] patients did not complete the study in the tiotropium group and 1358 in the control group (37 vs. 45%, $p < 0.001$). The major reason for discontinuation was adverse events (tiotropium 627 vs. placebo 746), which were mostly worsening of COPD, followed by consent withdrawal (300 vs. 403), non-compliance with the protocol (48 vs. 75), lost to follow-up (64 vs. 76) and others (61 vs. 58). Except for an initial steeper decline in the retention curve, discontinuation occurred in a nearly linear fashion throughout the study, however, the slope being steeper in the placebo group (Fig. 1).

Characteristics of completers and non-completers

The baseline characteristics of completers and non-completers are summarized in Table 1. As can be seen discontinuation was less frequent in GOLD stage II and more frequent in GOLD stage III and IV ($p < 0.0001$). The proportion of patients discontinued within a GOLD stage were: 36% Stage II, 49% Stage III, 13% Stage IV. The number of pack years smoked at baseline was greater in the non-completers ($p < 0.002$). Use of major respiratory medications both at baseline and during the study was not significantly different between completers and non-completers, except for inhaled anticholinergics at baseline. Pre-bronchodilator and post-bronchodilator FEV_1 were

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[f] Including one patient who received treatment for less than 45 months but was reported by investigator as a completer.

Table 1 Baseline characteristics in completers and non-completers. Means ± SD.

Characteristic	Completers	Non-completers	p	Completers	Non-completers	p
	Control	Control	Control	Tiotropium	Tiotropium	Tiotropium
number	1648	1358		1886	1100	
% male	76	71	0.0009	76	74	0.1796
GOLD II/III/IV	54/39/5	35/50/14	<0.0001	51/42/6	39/47/13	<0.0001
Age, yrs	64 ± 8	66 ± 9	<0.0001	64 ± 8	66 ± 8	<0.0001
Ex-/Current smokers	71/29	70/30	0.558	72/28	69/31	0.156
number of packyrs	47 ± 27	50 ± 29	0.0023	47 ± 27	52 ± 29	0.0002
COPD duration,y	10 ± 7	10 ± 7	0.492	10 ± 8	10 ± 7	0.315
Baseline LABA,%	59	61	0.287	60	60	0.779
Baseline ICS, %	61	63	0.419	61	63	0.384
Baseline AC, %	41	49	<0.0001	43	50	0.0006
FEV_1, pre-, L	1.18 ± 0.40	0.99 ± 0.38	<0.0001	1.14 ± 0.40	1.03 ± 0.40	<0.0001
FEV_1, pre-, %pred	42 ± 11	37 ± 12	<0.0001	41 ± 12	38 ± 12	<0.0001
FEV_1, post, L	1.41 ± 0.43	1.20 ± 0.42	<0.0001	1.38 ± 0.43	1.24 ± 0.44	<0.0001
FEV_1, post, %pred	50 ± 12	44 ± 13	<0.0001	49 ± 12	45 ± 13	<0.0001
FVC, post, L	3.19 ± 0.88	2.97 ± 0.91	<0.0001	3.15 ± 0.86	3.00 ± 0.87	<0.0001
FVC, post, %pred	90 ± 18	87 ± 19	<0.0001	89 ± 18	87 ± 19	0.0037
SGRQ, Total	43 ± 17	50 ± 17	<0.0001	44 ± 17	48 ± 16	<0.0001

significantly greater in completers whether expressed in liters or as a percentage of predicted ($p < 0.0001$ for both). A similar difference was seen for pre- and post-bronchodilator forced vital capacity (FVC). SRGQ total score was significantly higher, indicating worse health-related quality of life, in the non-completers than in the completers ($p < 0.0001$). Similar differences were observed for the three domain scores.

Treatment effects in completers and non-completers

Table 2 summarizes the treatment effects on the annual rate of decline of pulmonary function variables and SGRQ. Rate of decline of FEV_1 was significantly higher in non-completers than in completers. Similar differences were seen in the rate of decline of FVC and SVC. At each point in time during the trial including the baseline, FEV_1 was greater in the completers than in the non-completers e.g. in control, differences ranging from 180 to 250 mL for post-bronchodilator FEV_1 ($p < 0.0001$). Similar differences were seen for pre-bronchodilator FEV_1, pre- and post FVC, and pre- and post SVC.

Similarly, the annual rate of increase of the SGRQ total score during the trial was substantially greater in non-completers than in completers ($p < 0.0001$). Similar differences were seen for the three domain scores. The SGRQ total score was lower, indicating better quality of life, in completers than in non-completers at all points in time during the trial, e.g. the difference in the control group ranging from 5.9 to 10.8 units ($p < 0.0001$). Differences of similar magnitude were seen for the three domain scores. Treatment by completer status interaction did not reach statistical significance for any of the scores. Fig. 2 summarizes the SGRQ scores over time in the control and tiotropium groups, for completers and non-completers. As can be seen the difference between completers and non-completers clearly increased over time, suggesting that SGRQ under treatment was related to discontinuation as well.

Table 3 summarizes the data on exacerbations and resulting hospitalizations in completers and non-completers during the trial. Both in completers and non-completers, a significant reduction in the risk of an exacerbation and in the number of exacerbations per patient year were seen with tiotropium (hazard ratio or HR 0.89 and 0.86, both $p < 0.01$; rate ratio or RR 0.87 and 0.88, $p < 0.001$ and <0.03, respectively). Time to first hospitalization was

Table 2 Annual decline in FEV_1, FVC, SVC and SGRQ. For the lung volumes decline is expressed in mL $year^{-1}$ and for SGRQ in unitis.$year^{-1}$. Means ± SD.

| Characteristic	Completers	Non-completers	p	Completers	Non-completers	p
	Control	Control	Control	Tiotropium	Tiotropium	Tiotropium
Decline FEV_1, pre	30	38	0.023	29	41	0.002
Decline FEV_1, post	40	58	<0.0001	38	56	<0.0001
Decline FVC, pre	35	66	<0.0001	38	77	<0.0001
Decline FVC, post	53	106	<0.0001	54	112	<0.0001
Decline SVC, pre	37	71	<0.0001	42	88	<0.0001
Decline SVC, post	56	115	<0.0001	59	115	<0.0001
Decline SGRQ	1.05 ± 0.10	2.46 ± 0.25	$p < 0.0001$	1.04 ± 0.9	3.04 ± 0.26	$p < 0.0001$
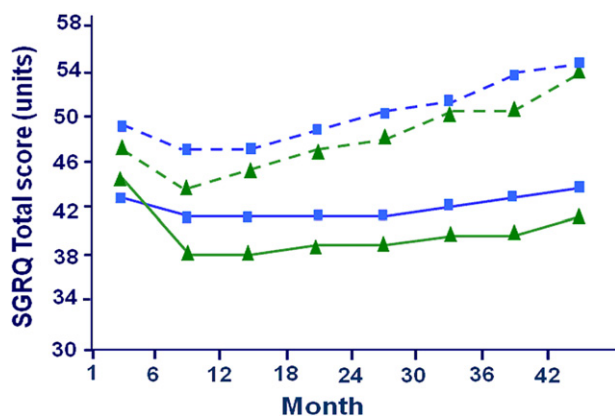
Figure 2 Evolution of the SGRQ score vs time in tiotropium (▲) and control (■), in completers (solid line) and non-completers (dashed line).

significantly prolonged in the tiotropium group among the non-completers only (HR 0.85, $p < 0.03$), whereas the number of hospitalizations per patient year was similar in the control and tiotropium groups in both completers and non-completers. For both treatment groups, the risk of an exacerbation was significantly smaller ($p < 0.0001$), the median time to first exacerbation significantly longer ($p < 0.0001$) and the number of exacerbations per patient year significantly lower ($p < 0.0001$) in completers than in non-completers. The risk of a hospitalization was smaller ($p < 0.0001$) and the number of hospitalizations per patient year was significantly lower ($p < 0.0001$) in completers compared with non-completers. The interaction of these variables with completer status did not reach statistical significance.

The number of fatalities observed on-treatment was 402 cases in the control group and 368 in the tiotropium group. Including the vital status information up to day 1470, the number of fatalities increased to 495 in the control group and 439 in the tiotropium group.

Model predicting discontinuation

Odds ratios with 95% confidence limits expressing the ratio completer/non-completer are shown in Table 4, for the whole group of patients. The following baseline variables were positively related to study completion: BMI, post-bronchodilator FEV_1, male gender and treatment with tiotropium. The following baseline variables were negatively related to completion: age, SGRQ, female gender, current smoking and assignment to the placebo group. Region did not contribute significantly to the model. The model fitting, however, was not sufficient ($R^2 = 0.1325$) to allow accurate prediction of drop-out.

Discussion

The present analysis of the UPLIFT study demonstrated that the discontinuation rates were substantial (36–45%) and significantly greater in the control group than in the active treatment group as observed in many COPD trials before.[1–8]

Table 3 Exacerbations/Hospitalizations. Times are expressed in months and numbers in numbers per patient year.

Characteristic	Completers Control	Non-completers Control	Completers Tiotropium	Non-completers Tiotropium	P Compl vs non-compl Control	P Compl vs non-compl Tiotropium	HR or RR Tio/control Completers	HR or RR Tio/Control Non-completers
Time to first Exacerbation, mo	16.47	8.90	20.11	10.74	<0.0001	<0.0001	0.89	0.86
Time to first Hospitalization, mo (25th percentile)	N/A	15.14	N/A	18.23	<0.0001	<0.0001	0.94	0.85
# Exacerbations/patient year	0.76	1.14	0.66	1.00	<0.0001	<0.0001	0.87	0.88
# Hospitalizations/patient year	0.11	0.34	0.11	0.31	<0.0001	<0.0001	1.05	0.93

Table 4   Odds ratio (95% CI) completer/non-completer.

Characteristic	Odds ratio	95% CI	p
Age	0.96	0.96–0.97	<0.0001
BMI	1.03	1.02–1.04	<0.0001
Post-BD FEV$_1$%	1.04	1.03–1.05	<0.0001
Pre-BD FEV$_1$%	0.99	0.98–0.99	0.037
SGRQ total	0.98	0.98–0.99	<0.001
Gender, F/M	0.83	0.73–0.95	0.007
Smoking, Current/Ex	0.75	0.66–0.86	<0.0001
Treatment C/Tio	0.69	0.62–0.78	<0.0001

Drop-out occurred in a nearly linear fashion as a function of time. The most important common reason for discontinuation was worsening of COPD. In general, patients discontinuing were older, had lower post-BD FEV$_1$ and BMI, poorer health status, more exacerbations and more pack years of smoking and were more likely to be current smokers and female, than patients completing the study.

Since this withdrawal rate is large and selective, it is expected to affect the treatment effects. It is generally believed that such a differential withdrawal rate tends to reduce the magnitude of the treatment effects.[3,6,8] Notwithstanding, Suissa recently demonstrated that in the Canadian Optimal trial,[12] patients with the lowest FEV$_1$ had the lowest decline and patients with the highest FEV$_1$ had the highest decline.[11] In the present dataset, this seems to be contradicted by the observation that discontinued patients tended to have higher rates of decline. The latter observation, however, needs to be interpreted with some degree of caution as these estimates are on average based on considerably fewer data points than in the completers.

Differential discontinuation poses a tremendous problem for the estimation of the effect size. Greenland et al. recently demonstrated, using the VA-exacerbation trial,[21] that the treatment effect of tiotropium on the probability of exacerbations was highly dependent upon the method of analysis used.[22] Indeed, even for this trial where discontinuation rates were only 8%, there were substantial differences in the estimated time to first event among the different analyses: ITT, on-treatment, per protocol and a nested G-estimation method. The first three conventional analyses all underestimated significant treatment effects. The ITT analysis estimated the prolongation of the time to first COPD exacerbation to be 21%, whereas the nested G-estimation method obtained an estimate of 31%. These differences are expected to be larger in trials with a greater degree of discontinuation and a longer duration such as UPLIFT.

Logistic regression analysis demonstrated that several baseline variables were significantly related to withdrawal. These included: age, FEV$_1$, BMI, health status, exacerbations, current smoking and gender. Although these factors were significantly related to withdrawal, the model fitting was not satisfactory (see above). This suggests that the relationships between these variables and withdrawal were – although statistically highly significant-not very tight. As a result, these variables probably do not permit the construction of models that will predict withdrawal precisely and hence, it will remain difficult to adequately correct treatment effects for the large withdrawal observed.

Along these lines it appears advisable in future trials to follow patients up who dropped-out from the trial and to perform the scheduled examinations in these patients. This is required to perform a valid ITT analysis.[23] The present trial also clearly demonstrated that on-treatment SGRQ score was an important predictor of discontinuation. This was also seen for decline in FEV$_1$. In general, it could be concluded that outcome variables appear to be important predictors of discontinuation and that the latter is not only determined by baseline variables.

The present trial also clearly demonstrated that significant mortality occurred in patients who withdrew from the trial and therefore, that it may not be optimal to base the demonstration of drug effects on mortality solely on the on-treatment population. In the present trial, the latter strategy would have led to an 18% underestimation of mortality rate or conversely, the true mortality rate was 21% higher than the on-treatment mortality rate, 23% in the control group and 19% in the tiotropium group. Since mortality has become a preferred outcome in COPD trials now,[6,8] this finding appears of great relevance for future trials. It further also supports the need for further follow-up of patients who withdrew from the trial as was done in the present trial and in the TORCH-study.[6] In the latter study, considerably more mortality occurred in patients who withdrew from the study than in the present study. Indeed, 411 of the 875 deaths or 47% of the deaths occurred in patients who withdrew from the study. In the UPLIFT study only 164 deaths out of 934 or 18%, occurred in patients who withdrew. There is no apparent explanation for this discrepancy, although differences in respiratory medication restrictions in each of the trials may have contributed to the observation.

The present analysis represents one of the first detailed analyses of the discontinuation phenomenon in a large long-term clinical trial. Similar observations were made by Calverley et al. with their analysis of withdrawal in the ISOLDE study.[24] They also found a lower baseline FEV$_1$, greater rate of decline of FEV$_1$, and faster decline in health status in patients withdrawing from this trial. The strengths of the present trial include rigorous data capture, size (5993 patients), long duration of follow-up (4 years), the completeness of the outcomes studied (pulmonary function, health status, exacerbations, resulting hospitalizations and mortality) and the independent adjudication of causes of death. The most relevant limitation is that except for vital status, no follow-up was provided for the patients who prematurely discontinued from the trial (see above).

As a consequence, the information available for these patients, particularly the rate of decline data, is based on considerably fewer data points than for the completer population. In future trials, provision for complete follow-up of the drop-out patients who survived to the end of the treatment period would provide us with considerably more complete information on these patients. However, it is recognized that following patients after discontinuation of study medication is logistically and ethically challenging. The latter would be the case with a patient who would refuse all further follow-up after withdrawal. A compromise that might be considered could be that at least follow-up data would be obtained at the end of the anticipated treatment period in all patients.

In conclusion, in the present large scale clinical trial discontinuation rates were substantial and, greater in the placebo group than in the active treatment group. Discontinuation occurred in a nearly linear fashion. The prime baseline factors associated with a greater probability of discontinuation were older age, lower FEV_1, lower BMI, poorer health status, current smoking and female gender. On-treatment variables were important determinants of discontinuation as well. It therefore appears advisable that longer term clinical trials consider follow-up of patients who prematurely discontinue trial participation.

Acknowledgments

Conflict of interest

Marc Decramer: Lecturer on sponsored symposia for Boehringer and Pfizer, Consultant for GSK, Dompé, Zambon, Boehringer and Pfizer, Advisory Board GSK, Astra Zeneca, Novartis, Nycomed, No stock holdings in pharmaceutical industry.

Supplementary material

Supplementary data associated with this article can be found, in the on-line version, at doi:10.1016/j.rmed.2011.04.002.

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