Withdrawal From Treatment as an Outcome in the ISOLDE Study of COPD*

Peter M. A. Calverley, MD; Sally Spencer, BSc; Lisa Willits, PhD, MSc; P. Sherwood Burge, MD; and Paul W. Jones, MD; on behalf of the ISOLDE Study Group

Objectives: **To investigate the determinants of patient withdrawal from our study, and the effect of these withdrawals on the outcome of treatment with inhaled corticosteroids in patients with COPD.**
Design: **A double-blind, placebo-controlled, randomized trial.**
Setting: **Eighteen outpatient centers in the United Kingdom.**
Participants: **Seven hundred fifty-one patients with stable COPD defined clinically and as baseline postbronchodilator $FEV_1 \geq 0.8$ L and < 85% predicted, FEV_1/FVC ratio < 70%, and FEV_1 change after albuterol < 10% of predicted.**
Intervention: **Random assignment of either 500 μg bid of inhaled fluticasone propionate (FP) using a spacer device or an identical placebo inhaler. Treatment was continued for 3 years or until patients withdrew from follow-up.**
Measurements and results: **Postbronchodilator FEV_1 was measured on three occasions before randomization and every 3 months thereafter. Health status was assessed by the disease-specific St. George Respiratory Questionnaire (SGRQ) and the modified short-form 36 questionnaire (SF-36) at baseline and every 6 months. Three hundred thirty-nine patients withdrew, of whom 156 patients received FP. Prescription of frequent courses of oral prednisolone was the most common reason for withdrawing as specified in the protocol (69 patients in the FP group withdrew due to respiratory symptoms, compared with 93 patients in the placebo group). This explained the significantly greater dropout of placebo-treated patients that was most evident when FEV_1 was < 50% predicted. Patients withdrawing had a significantly more rapid decline in health status, measured by both the SGRQ and the SF-36 ($p < 0.001$). Those withdrawing from the placebo group had a more rapid decline in FEV_1 and more exacerbations than the FP-treated groups. Baseline FEV_1 was lower in dropouts than in patients completing the study receiving placebo, but there was no difference between the respective groups receiving FP.**
Conclusions: **Patients who withdrew from follow-up were those with the most rapidly deteriorating health status and lung function. Losing these patients from the final analysis can reduce the power of a study to achieve its primary end point.** ***(CHEST 2003; 124:1350–1356)***

Key words: COPD; exacerbation; fluticasone propionate; patient withdrawal

Abbreviations: FP = fluticasone propionate; ISOLDE = Inhaled Steroids in Obstructive Lung Disease; SF-36 = modified short-form 36 questionnaire; SGRQ = St. George Respiratory Questionnaire

In most areas of pulmonary medicine, treatment is based on the results of carefully conducted, randomized controlled trials. In diseases such as bronchial asthma, brief periods of follow-up are sufficient to evaluate the effect of most drugs, including those that modify the natural history of the disease.[1,2] Treatment trials commonly last from 3 to 12 months; in addition to conventional outcomes such as changes in pulmonary function, symptoms, or health status, the number of patients who withdraw from follow-up and

*From University Hospital Aintree (Dr. Calverley), Liverpool; St. George's Hospital Medical School (Ms. Spencer and Dr. Jones), London; Heartlands Hospital NHS Trust (Dr. Burge), Birmingham; and GlaxoSmithKline (Dr. Willits), Stockley Park, UK.
Drs. Calverley, Burge, and Jones, and Ms. Spencer were all independent investigators in the ISOLDE study from which this work is derived. This study was supported by a grant from GlaxoSmithKline. Ms. Willits is a statistician working for GlaxoSmithKline. The investigators had unrestricted access to the data and determined its analysis throughout the study.

Manuscript received September 17, 2002; revision accepted April 14, 2003.

Correspondence to: Peter M. A. Calverley, MD, Department of Medicine, The University Hospital Aintree, Clinical Sciences Centre, Longmoor Lane, Liverpool L9 7AL, United Kingdom; e-mail: pmacal@liverpool.ac.uk

their reasons for doing so are reported.[3,4] This patient dropout information provides further useful information about the effectiveness and acceptability of treatment.

Evaluating therapy in patients with COPD usually takes longer, although drugs such as long-acting inhaled β-agonists can modify health status within 16 weeks.[5] Changes in disease progression and, particularly in the rate of decline of FEV_1, are harder to assess, and should be monitored over at least 3 years. There is general agreement that it is difficult to do this in < 3 years, the minimum period chosen in a series of intervention studies[6–9] using inhaled corticosteroids. Maintaining follow-up over 3 years poses significant problems, as COPD is characterized by exacerbations of disease that can lead to study withdrawal from the study. Patient withdrawal due to exacerbations is a particular problem when studying inhaled corticosteroids, as courses of oral corticosteroids are the most effective way of speeding the resolution of exacerbations[10,11]; however, if these courses are administered frequently, the outcome of the trial may be affected.

Patient withdrawal is not a problem when patients are studied early in the natural history of the disease when exacerbations are infrequent.[6,7] The Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study recruited patients with established disease. To show a treatment effect, it was important to retain the patients within the trial for as long as possible. The intention-to-treat analysis of this study has now been reported.[8] In this article, we examine the characteristics of those patients who withdrew from the trial, and the effect the withdrawals had on our study population and how we analyzed the data. We believe that these data are relevant to future investigators who study patients of a similar severity, in which patient behavior during long-term follow-up can be very different from patients with milder disease.

Materials and Methods

Patients

Details of the trial design and patient recruitment have been presented previously.[8] All patients had a clinical diagnosis of nonasthmatic COPD, met the established diagnostic criteria for this disorder,[12,13] were aged 40 to 75 years inclusive, and had a history of current or previous smoking. At baseline, postbronchodilator (400 μg albuterol) FEV_1 was ≥ 0.8 L and < 85% predicted, (FEV_1/FVC) ratio was < 70%, and the FEV_1 change after albuterol was < 10% of predicted. Patients with a clinical diagnosis of asthma, those requiring any nontrial anti-inflammatory treatment for lung disease or β-adrenergic blockers, patients with a life expectancy < 5 years due to concomitant disease, and those unable to meet the required standards for spirometry at the pretrial visit were excluded. Nasal and ocular topical corticosteroids were allowed, as were methylxanthines and long-acting inhaled bronchodilators. All patients received albuterol, 200 μg, and ipratropium bromide, 80 μg, as required throughout the trial. The protocol was approved by the ethical review committee of each participating center, and all subjects gave written informed consent.

Spirometric Measurements (FEV_1 and FVC)

Measurements were made at the same time of day for each subject. Short-acting bronchodilators were withheld for 4 h, oral or long-acting bronchodilators for 12 h, caffeine-containing products for 4 h, smoking for 2 h, and large meals for 1 h prior to spirometric measurements. Measurements were made with patients in the seated position after 15 min of resting. Spirometry was performed before bronchodilation, and then 30 min after treatment with 80 μg of ipratropium bromide and 400 μg of albuterol.

Health Status Measurement

The St. George Respiratory Questionnaire (SGRQ) is a supervised self-administered measure, designed specifically for use in airways disease.[14] It is a 50-item survey from which a total of three component scores are calculated: symptoms (distress caused by specific respiratory symptoms), activity (physical activities that cause or are limited by breathlessness), and impacts (social and psychological effects of the disease). The SGRQ is scored from 0 to 100, where 0 indicates best health and 100 indicates worst health. A change in score of 4 U is consistent with a clinically significant change in the patient[15,16]; therefore, an increase in score indicates worsening health status. The SGRQ has been shown to be a valid measure of health impairment in patients with chronic airflow limitation, and to respond to change with therapy.[5,14,17]

General health status was assessed using the SF-36, a core generic measure.[18] It is a self-completed questionnaire containing 36 questions covering eight health concepts: physical function, physical role limitation, mental role limitation, social function, mental health, pain, energy/vitality, and health perception. Two summary components (physical and mental) can also be calculated by differentially weighting the scales. The SF-36 scales are scored as a percentage of impairment, with 0 representing worst health and 100 indicating best health. With this scale, a decrease in score indicates worsening general health. Its reliability is extensively documented.[19]

Other Baseline Measurements

Smoking history was validated with exhaled breath carbon monoxide and urinary cotinine measurements. Smokers were defined as those currently smoking or with a urinary cotinine level > 40 ng/mL. Ex-smokers were those who had given up smoking, and had a urinary cotinine level < 40 ng/mL Gas transfer was measured using the single-breath method. Skin-prick tests with diluent control, 10% histamine, and allergen extracts of *Dermatophagoides pteronyssinus*, cat dander, mixed grass pollens, and *Aspergillus fumigatus* were read at 15 min. Maximum wheal diameters were measured, and atopy was defined as a > 3 mm-wheal to at least one allergen extract with appropriate controls.

Protocol

After completing an 8-week run in period to establish clinical stability and confirm the postbronchodilator spirometry values on

three occasions, patients were offered a 2-week trial of oral corticosteroids (0.6 mg/kg/d) prior to commencing 3 years of trial medication. Treatment was randomized between 500 μg of fluticasone propionate (FP) or an identical placebo bid from a metered-dose inhaler using a Volumatic spacer device (Allen and Hanbury; Greenford, Middlesex, UK). The patients re-attended were followed at 3-month intervals when postbronchodilator spirometry was recorded, and every 3 months thereafter together with a detailed account of all new symptoms and disease exacerbations. These exacerbations were defined as worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics and/or oral corticosteroids. Health status was recorded at baseline and every 6 months thereafter.

Criteria for Withdrawal

Patients were permitted to withdraw at any time during the study at will or at the discretion of their physician. Reasons for withdrawal were categorized into those that were respiratory and related to the underlying COPD and into other medical and social reasons leading to the discontinuation of follow-up. Patients who were treated by their family physician with a course of oral corticosteroids on three occasions during any 3-month period were withdrawn as per protocol, automatically considered as a study dropouts, and offered open-label therapy with inhaled corticosteroids. Further follow-up of these patients was not undertaken.

Data Analysis

Patients in whom 3 years of follow-up data were available from the time of randomization were considered to be completers; all other randomized patients were classified as noncompleters. Student *t* tests were used to analyze differences in mean values between treatment groups. A Kaplan-Meier plot was used to compare the time to withdrawal between treatment groups. The Fisher exact test compared treatment withdrawals by baseline FEV_1. A random coefficients hierarchical model, described elsewhere,[8] was used to determine the rates of change in FEV_1 and health status for patients who completed the study and those who withdrew. Data are expressed as mean (SD) unless stated otherwise stated. Baseline FEV_1 is the mean of data measured at 4 weeks and 8 weeks of the run-in period. Tests were two sided, with a 15% level of significance to take into account multiple comparisons.

Results

Demographic and Baseline Characteristics

The demographic and baseline characteristics of the patients categorized into those completing and withdrawing and by treatment allocation are presented in Table 1. At the beginning of the study, there were no significant differences in gender, atopy, smoking status, or pack-years of tobacco exposure between any of these groups; however, patients who withdrew while receiving placebo were significantly more likely to have been receiving inhaled corticosteroids before entry into the trial. The baseline FEV_1 data did not differ between patients who did and did not withdraw in the FP group, but was lower in those withdrawing from placebo. This was different at the 5% significance level, but did not meet our *post hoc* criterion for statistical significance.

Reasons for and Time to Withdrawal

Of the 751 patients randomized, 402 patients successfully completed the 3-year follow-up, of whom 220 patients had received inhaled FP. The most common reasons for withdrawal were respiratory events (n = 69, FP group; n = 93, placebo group), the majority being frequent exacerbations as

Table 1—*Demographic and Baseline Characteristics

	FP (n = 376)		Placebo (n = 375)	
Characteristics	Completed 3 yr (n = 220)	Withdrawn Prior to 3 yr (n = 156)	Completed 3 yr (n = 182)	Withdrawn Prior to 3 yr (n = 193)
Age, yr	63.2 (6.8)	64.5 (7.5)	62.8 (7.1)	64.6 (7.0)
Male gender, %	75	76	71	77
Atopy, %	26	29	24	24
Continuous smokers, %	34	40	38	40
Continuous ex-smokers, %	46	47	46	46
Smoking pack-yr	44.4 (28.8)	44.3 (31.2)	42.7 (31.2)	45.0 (36.7)
TLCO, mmol/min/kPa	4.95 (2.08)	4.62 (2.04)	5.28 (2.14)	4.38 (2.03)
KCO, mmol/min/kPa/L	1.02 (0.64)	0.98 (0.66)	1.08 (0.50)	0.90 (0.48)
Previous use of regular inhaled corticosteroids, %	52	50	†50	†64
Baseline postbronchodilator FEV_1, L	1.42 (0.47)	1.43 (0.48)	1.47 (0.50)	1.34 (0.47)
Baseline % predicted postbronchodilator FEV_1, L	49.8 (14.9)	51.3 (15.1)	52.0 (14.6)	48.2 (15.4)

*Data are presented as mean (SD) unless otherwise indicated. TLCO = diffusing capacity; KCO = diffusion coefficient.
†$p < 0.01$ between identified groups (Fisher exact test).

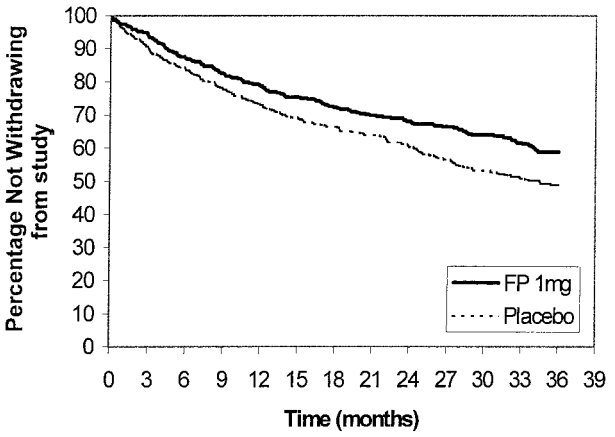

FIGURE 1. Kaplan-Meier plots of the number of patients remaining in the study in both FP and placebo groups, and patient survival allowing for withdrawal from all causes.

defined in the protocol. Thirty-five patients withdrew due to cardiac events, and 30 patients withdrew due to the development of a malignancy. Forty-nine patients either admitted to not taking any study medication or failed to return for follow-up. The remaining patients withdrew due to a variety of other individually infrequent adverse events or for social reasons. There was no difference in the frequency of nonrespiratory withdrawals between the two groups ($p > 0.5$). The time to withdrawal from all causes in placebo- and FP-treated patients is illustrated by the Kaplan-Meier plot in Figure 1. Patients withdrew steadily throughout the study. At all time points, more patients withdrew while receiving placebo at each time point. The median number of exacerbations during FP treatment was 0.99/yr irrespective of subsequent withdrawal. In those receiving placebo, it was 1.05/yr in those completing but 1.69/yr in those who did not complete the trial ($p = < 0.02$).

Spirometry and Withdrawal

The study population was separated into two groups on the basis of an FEV_1 of $< 50\%$ predicted (American Thoracic Society stage 3). In patients with a higher FEV_1, the number of patients completing and withdrawing during the study were similar in patients with a higher FEV_1 ($> 50\%$ predicted), with 46% of the total withdrawing. When the FEV_1 was $< 50\%$ predicted, there was a clear difference between the two treatments, with significantly more patients withdrawing from placebo compared with FP treatment (57% vs 38%, respectively; $p = 0.0002$). The reasons for withdrawal were similar in each group as a percentage of the total causes listed, but the absolute numbers were lower in the FP-treated patients.

The rate of decline in FEV_1 is presented in Figure 2. The effect of treatment on the rate of decline in FEV_1 was the same in patients who withdrew and those who completed the study (Table 2, Fig 2); however, patients who completed the study had a significantly slower decline in FEV_1 than those who withdrew, irrespective of treatment group ($p < 0.02$).

Health Status and Withdrawal

Baseline health status data for the SGRQ and SF-36 were similar in all domains at study entry irrespective of subsequent withdrawal. The rate of decline of health status in those withdrawing in the FP group did not differ from that in the placebo completers (Table 2). In contrast, the deterioration

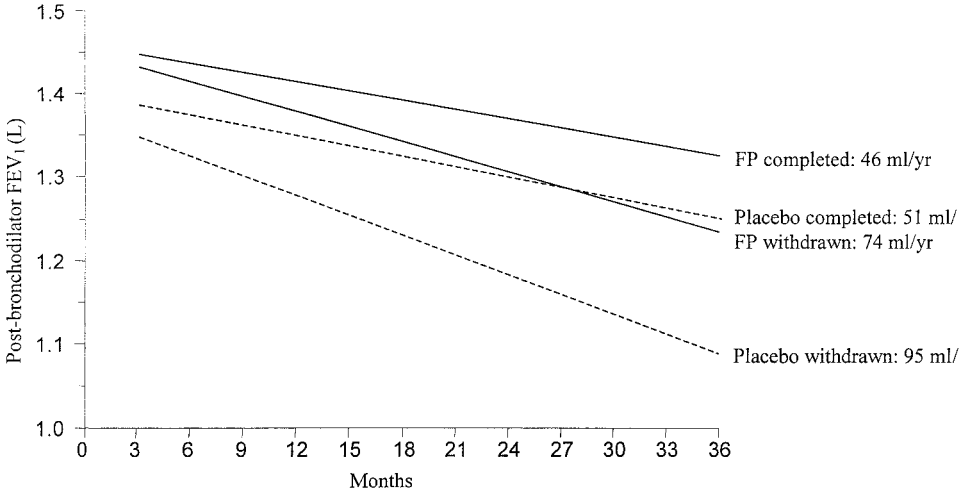

FIGURE 2. Mean rate of change of the postbronchodilator FEV_1 over 3 years in patients receiving placebo who withdrew and completed the study, and those receiving FP who withdrew and completed the study.

Table 2—*Decline in Postbronchodilator FEV_1 and Health Status

Variables	FP			Placebo		
	Completers (n = 211)	Withdrawers (n = 107)	p Value	Completers (n = 175)	Withdrawers (n = 123)	p Value
Postbronchodilator FEV_1	46 mL/yr (n = 220)	74 mL/yr (n = 119)	< 0.02	51 mL/yr (n = 181)	95 mL/yr (n = 144)	< 0.02
SGRQ total	2.00	2.79	0.4	2.65	6.74	0.0001
SGRQ symptoms	1.15	0.64	0.6	1.99	4.81	0.009
SGRQ activity	2.04	3.86	0.08	3.06	7.02	0.0001
SGRQ impacts	2.21	2.80	0.6	2.63	7.35	0.0001
SF-36 physical function	− 1.81	− 2.40	0.6	− 2.82	− 7.10	0.0001
SF-36 physical role	− 3.23	− 3.64	0.9	− 4.47	− 11.06	0.005
SF-36 pain	− 1.25	− 3.55	0.2	− 2.31	− 2.08	0.8
SF-36 health perception	− 2.49	− 2.28	0.9	− 2.25	− 7.10	0.0001
SF-36 energy/vitality	− 1.22	− 2.43	0.3	− 2.07	− 5.59	0.001
SF-36 social function	− 1.22	− 2.43	0.3	− 2.07	− 5.59	0.001
SF-36 mental role	− 4.51	− 6.08	0.6	− 5.40	− 7.82	0.4
SF-36 mental health	− 0.02	− 0.32	0.8	− 0.99	− 2.78	0.06

*Data are presented as U/yr unless otherwise indicated.

in SGRQ total, symptoms, and impacts scores of placebo-treated patients who withdrew was significantly greater than that of placebo completers or the patients treated with FP ($p < 0.01$). The total SGRQ score of patients withdrawing from placebo deteriorated at 6.74 U/yr, equivalent to a clinically noticeable deterioration in health status every 8 months (Fig 3). The rate of change in the SF-36 physical function and health perception scores in placebo-treated patients who withdrew was greater compared to the other three groups ($p < 0.001$).

Discussion

This is the first prospective COPD study in which large numbers of patients failed to complete the intended follow-up period because of nonrandom withdrawal. Like other studies[6–9] of inhaled corticosteroids, our trial did not show a significant effect on the primary outcome measure, rate of decline of FEV_1; however, patients withdrawing from our study had a more rapid deterioration in lung function and health status assessed prior to withdrawal. Loss of these patients from the trial is likely to have reduced the power of the investigation to show differences between groups, and suggests that the effects that were reported are a conservative estimate of the impact of treatment.

At randomization, there were no significant differences between the treatment groups. During the trial, almost half the patients withdrew, principally due to their need for repeated courses of oral

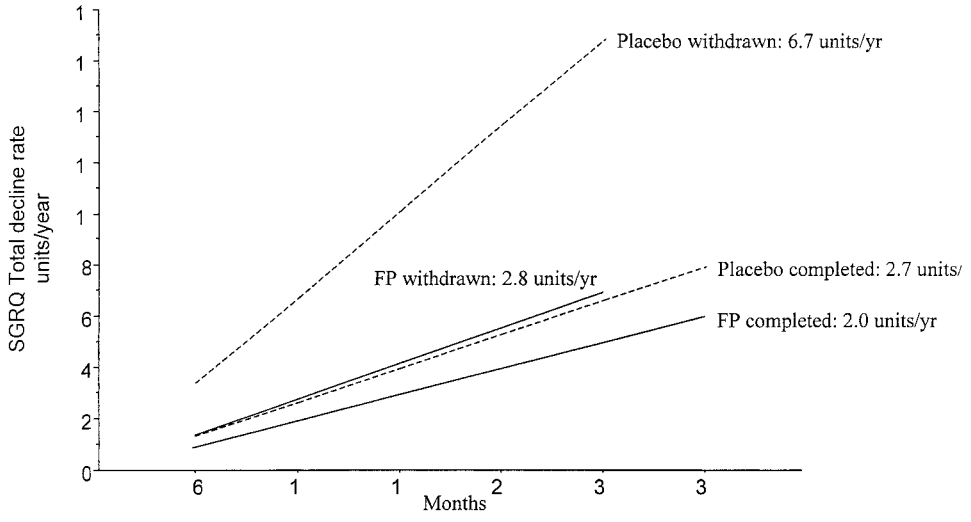

Figure 3. Mean rate of change of the SGRQ total score over 3 years in patients receiving placebo who withdrew and completed the study, and those receiving FP who withdrew and completed the study. An increase in score represents worsening of health status.

corticosteroids. This withdrawal due to repeated oral corticosteroid use was more common in placebo-treated patients, and explains the different dropout rates in between the groups. *Post hoc* categorization of patients into completers and withdrawers suggests an explanation for the different dropout rates in the FP- and placebo-treatment groups. Placebo-treated patients who withdrew had a tendency to have a lower initial FEV_1 than those who completed 3 years of follow-up, a finding not seen in FP-treated patients. The effect of the inhaled corticosteroid may have been to allow these more physiologically impaired patients to better cope with exacerbations better, and avoid treatment with oral corticosteroids. Although patients who had previously received inhaled corticosteroids were no different in other respects at study entry,[8] they were more likely to withdraw if randomized to placebo, which is in keeping with other data from the prerandomization phase of this study.[20]

The severity of COPD assessed spirometrically also influenced both the number withdrawing and the number of exacerbations that occurred. Patients with worse spirometric findings were more likely to withdraw and have exacerbations, and this influenced the ability of treatment to show an effect. Thus, the effect of FP treatment on respiratory withdrawals was most evident in patients with more severe disease (American Thoracic Society stage 3, *ie*, $< 50\%$ predicted FEV_1), where 104 patients withdrew due to respiratory causes compared with the 54 patients in the less severely affected groups. These data explain the lower frequency of exacerbations in other trials of inhaled corticosteroids,[6,7] where the baseline FEV_1 was higher. Selection of patients by a specified postbronchodilator FEV_1 is therefore likely to be important when exacerbation frequency is a study outcome. Moreover, the patient who withdrew were those in whom the FEV_1 was declining most rapidly, providing objective confirmation of their greater disease severity.

Health status measurements, whether disease specific or generic, deteriorate in patients with COPD, and this change is less marked in those treated with inhaled corticosteroids.[21] Our analysis shows that an important consequence of effective treatment is to prevent the deterioration in health status in those who would otherwise withdraw. Thus, the health status change of patients receiving FP who withdrew was similar to that in the placebo-treated completers. Impaired health status is associated with increased health-care utilization[22] and increased numbers of exacerbations.[23] The higher median exacerbation frequency in those withdrawing while receiving placebo suggests that exacerbations contribute to their accelerated decline in health status, and the protective effect of FP arises from the lower number of exacerbations observed with this drug.

Differential withdrawal from the study might modify the study outcome. The loss of those patients with the most rapid decline in FEV_1 will reduce the overall power of the study to show a difference. The "healthier survivor" effect seen in the placebo-treated but not the FP-treated patients may reduce the difference between groups in the rate of decline of FEV_1. This may be important because, as others, we used a random effects model to estimate the rate of decline of FEV_1, but this is a conservative approach to detecting differences between treatments, especially if there are differential dropout rates between treatment groups. A theoretical analysis of the magnitude of this effect is shown in Figure 3. Differential dropout rates between treatment groups is a relevant consideration for other potential disease-modifying agents, in which a reduction of exacerbations may also occur and similar problems arise.

Avoiding premature withdrawal is clearly a difficult problem in any study in which an active therapy is compared with a placebo treatment. This is especially so when the treatment is already prescribed by some physicians, and its removal can precipitate an exacerbation.[20] Patients withdrawn should continue to be followed up even if their medication is changed, and future trials should consider less rigorous criteria than those used here to determine when a patient should be discontinued from participating in the study.

Reporting the number of patients leaving a clinical trial provides useful additional information about treatment effectiveness in bronchial asthma,[3,4] and our data suggests that this is also true for COPD. The significantly different outcomes in those withdrawing from active and placebo treatment suggests that an important clinical effect is occurring. Thus, the impact of inhaled corticosteroids in COPD may be rather greater than analyses of individual end points have so far suggested. These benefits are most marked in patients with an $FEV_1 < 50\%$ predicted, and as such are in line with recommendations for treatment suggested in the Global Initiative for Chronic Obstructive Lung Disease management strategy.[13]

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