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Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations

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ABSTRACT: Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with worse health and increased healthcare utilisation. The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study in COPD showed a 26% reduction in the yearly rate of exacerbations in patients treated with fluticasone propionate (FP) compared to placebo, but did not indicate which patients showed greatest benefit.

In this study the patients were stratified into mild and moderate-to-severe COPD using the American Thoracic Society criterion of forced expiratory volume in one second (FEV1) 50% predicted, and the total number of exacerbations and those requiring treatment with oral corticosteroids were examined.

There were 391 (195 FP) patients with mild COPD and 359 (180 FP) patients with moderate-to-severe disease. The exacerbation rate was highly skewed in mild disease, but more normally distributed in moderate-to-severe disease. FP reduced the overall exacerbation rate in moderate-to-severe disease (FP median rate 1.47 yr^{-1}, placebo 1.75 yr^{-1}), but not in mild disease (FP 0.67 yr^{-1}, placebo 0.92 yr^{-1}). FP use was associated with fewer patients with $\geqslant$1 exacerbation·yr^{-1} being treated with oral corticosteroids (mild: FP 8%, placebo 16%; moderate-to-severe: FP 17%, placebo 30%).

Effects of fluticasone propionate on exacerbations were seen predominantly in patients with a postbronchodilator forced expiratory volume in one second <50% predicted. These data support recommendations in the Global Initiative for Chronic Obstructive Disease treatment guidelines that inhaled corticosteroids should be considered in patients with moderate-to-severe chronic obstructive pulmonary disease who experience recurrent exacerbations.

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Exacerbations in chronic obstructive pulmonary disease (COPD) are common and associated with significant impairment of health status [1]. Hospitalisation is relatively frequent [2]. The total cost of treating exacerbations of COPD in the USA has been reported to be US$ 1.2 billion, with inpatient and outpatient care accounting for US$ 32 million and US$ 452 million, respectively [3].

International guidelines recommend bronchodilators as first-line treatment for COPD symptom control [4–6], since there no evidence to suggest that such agents slow the progression of the disease [7]. Studies with inhaled corticosteroids have failed to show a reduction in rate of decline in forced expiratory volume in one second (FEV1) in COPD [8–13]. By contrast, there is evidence to suggest that these agents may reduce the rate and severity of COPD exacerbations defined clinically and by the use of additional treatment [8, 11].

The recent Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, investigated the effect of inhaled fluticasone propionate (FP) 500 μg twice daily for 3 yrs on the rate of decline of FEV1 and other clinical outcomes [12]. FP treated patients had a significantly greater postbronchodilator FEV1 than placebo throughout the trial, although the rate of decline in FEV1 was not altered. FP did reduce the median yearly exacerbation rate by 25% and significantly reduced the rate of deterioration in health status. The initial report presented the intention-to-treat analysis of these data, but did not consider whether all patients showed similar treatment benefits. In this study a *post hoc* analysis to determine whether existing criteria for disease severity identifies patients with a different probability of exacerbating and whether the effect of inhaled corticosteroids on acute exacerbations is influenced by disease severity are reported.

Methods

Full details of the study methodology, patient selection, efficacy assessments and statistical analyses have been published previously [12].

Patients

In brief, the study enrolled current or former smokers aged 40–75 yrs with nonasthmatic COPD. Patients were excluded due to the following: they had ever received a diagnosis of asthma, FEV1 improved by >10% predicted normal following 400 μg inhaled salbutamol, the postbronchodilator FEV1 was <0.8 L at study entry or they had clinically significant concurrent medical conditions or a condition likely to reduce life expectancy to <5 yrs.

Study design

The study used a randomised, double-blind, placebo-controlled, parallel-group design. It was conducted in 18 hospitals in the UK. All patients provided written informed consent and the protocol was approved by each local research ethics committee.

Patients using inhaled corticosteroids discontinued them and all entered an 8 week-run-in period to ensure clinical stability and establish the baseline pre- and postbronchodilator spirometry. After this, patients were asked to participate in a 2-week trial of oral corticosteroids (0.6 $mg \cdot kg^{-1} \cdot day^{-1}$). The majority did so (85%), but those who did not proceeded directly into the randomised study. Classification of patient severity was made using FEV1 measurements obtained before any corticosteroid was given.

Patients were withdrawn from the study if continuance was considered detrimental to the patient or if they required more than two short courses of oral corticosteroids in any 3-month period or maintenance oral or inhaled corticosteroid treatment.

Treatment

At the end of the run-in period, patients were randomised to receive FP 500 μg twice daily *via* metered-dose inhaler and Volumatic™ (GlaxoSmithKline, Greenford, UK) spacer device or an identical placebo. Randomisation was carried out centrally using a computer program and treatment allocation codes were not available to the trialists. Other medication was continued throughout the study and was equally distributed in terms of dose of drug and frequency of use between the treatment groups.

Efficacy

The principal outcome in this analysis was the number of exacerbations per year. An exacerbation was defined as "chest problems requiring treatment with antibiotics and/or oral corticosteroids". It had been anticipated that, in this 3-yr study the great majority of exacerbations would be treated by primary care physicians and it was judged to be impossible to set criteria for the diagnosis of an exacerbation to be used by several hundred primary care physicians. Exacerbations were recorded by patient self-report at 3-monthly intervals. Treatment of each exacerbation was recorded, specifically whether the attending doctor prescribed antibiotics, oral corticosteroids or both. The physician treating these episodes was unaware of the trial treatment the patient was receiving.

Statistical analysis

The results were analysed first in the intention-to-treat (ITT) population (defined as all patients who were randomised to treatment and who received at least one dose of study medication), then in two subgroups, categorised on the basis of the American Thoracic Society criteria for severity [4] as follows: mild (postbronchodilator FEV1 $\geq$50% pred) and moderate-to-severe (postbronchodilator FEV1 <50% pred).

The exacerbation rate for each patient was calculated as the number of exacerbations experienced per year. If a patient withdrew during the study, the exacerbation rate was calculated by dividing the number of exacerbations experienced during the treatment period by the time spent on treatment. Exacerbations were analysed as follows: 1) all exacerbations regardless of how treated; or 2) exacerbations treated with oral steroids, either alone or in combination with antibiotics. The difference between treatments was tested using the van Elteren extension to the nonparametric Wilcoxon Mann-Whitney rank-sum test [14]. Study centre was used as a stratifying variable in the analysis. Confidence intervals (CI) for treatment differences were calculated by pooling all the treatment differences using the Hodges-Lehman method [15]. Stratification by study centre was not considered in this calculation.

The effect of treatment on the proportion of patients experiencing one or more exacerbations in each year of the study (cumulative) was tested using Fisher's exact test [16]. The relationship between treatment and time to onset of the first exacerbation was analysed using survival analysis techniques and the log-rank test (5% significance level). The time to the first exacerbation was also modelled using Cox's proportional hazards model [17]. The covariates considered for inclusion in the model were age, smoking status, sex, study centre and baseline FEV1. Distribution statistics for parametric data are reported as SD.

Results

Patient demography

A total of 751 patients were randomised to treatment, 376 to FP and 375 to placebo.

Both treatment groups were well matched at baseline [12]. The baseline and demographic data were similar for patients with mild and moderate-to-severe COPD (table 1). There were small differences between the two subgroups, with significantly more males than females with mild rather than moderate-to-severe disease (85 *versus* 65%, p<0.0001). The number of pack-yrs smoked was higher in the moderate-to-severe

Table 1. – Patient characteristics at baseline

Characteristics	Moderate-to-severe FEV_1 <50% pred		Mild FEV_1 ⩾50% pred	
	Placebo	FP	Placebo	FP
Subjects n	195	196	179	180
Age yrs	64±7	64±6	63±8	63±8
Male %	81	86	66	63
Smoking history				
Pack-yrs	48±36	47±30	39±31	42±30
Current smokers %	38	32	41	41
Exsmokers %	48	51	44	43
Intermittent %	14	17	16	16
Atopy[#] %	14	13	11	14
FEV_1[¶] L	1.0±0.2	1.0±0.3	1.6±0.5	1.6±0.5
FEV_1 % pred	39±8	39±8	62±10	62±10
% FEV_1 reversibility[+]	4.1±3.4	4.2±3.4	4.8±3.4	4.6±3.6

Data are presented as mean±SD; FEV_1: forced expiratory volume in one second; FP: fluticasone propionate; % pred: % predicted; [#]: atopy defined as positive skin-prick test to one or more common allergens; [¶]: prebronchodilator FEV_1; [+]: change in FEV_1 after bronchodilator expressed as % pred. There were no significant differences ($p>0.05$) between the treatment groups, within each severity category, for any variable. Except for proportionally more females in the mild compared to the moderate-to-severe group ($p<0.001$) and more pack-yrs smoked in the moderate-severe group.

group than in the mild group (47 *versus* 41, $p<0.01$), but the proportion of continued, mixed and exsmokers was the same in the two groups ($p>0.05$).

Onset of first exacerbation

Kaplan-Meier analysis of the ITT population showed no difference in the time to first exacerbation, p=0.34. Using Cox's proportional hazards model for the time of onset of the first exacerbation, the median time in the placebo group was 136 days *versus* 164 days in the FP group (95% CI 0.79–1.09, p=0.35).

Number of exacerbations and withdrawals

Analysis of the total number of exacerbations showed no significant difference between the two treatment groups. During the first year of treatment, 227 patients in the FP group (61%) and 237 in the placebo group (64%) had at least one exacerbation. Similarly, 290 (78%) and 286 (77%) patients, respectively, experienced at least one exacerbation during the 3-yr study period. During the study, 355 patients were withdrawn, 160 in the FP group and 195 in the placebo group. The most common reason for withdrawal was frequent exacerbations of COPD; 42 FP patients, 54 placebo patients. Placebo-treated patients were also more likely to be withdrawn earlier than FP patients [12]. As a result of the earlier and greater drop-out rate, placebo patients spent less time in the study (758 patient-yrs) than those treated with FP (840 patient-yrs).

Frequency of exacerbations

The annualised rate of exacerbations ranged from 0 to ⩾8 yr^{-1}. The distribution was highly skewed in the mild patients, but more normally distributed in those with moderate-to-severe disease. Over the 3-yr period, 29% of the mild patients had no exacerbations at all, but this was seen in only 16% of those with moderate-to-severe disease (fig. 1). The median exacerbation rate in the combined treatment groups was significantly lower in the mild patients (0.93 yr^{-1}) compared to those with moderate-to-severe disease (1.64 yr^{-1}), $p<0.0001$.

In the ITT population, there were fewer exacerbations in the FP-treated group (0.99 exacerbations·yr^{-1}) compared with placebo (1.32 exacerbations·yr^{-1}), p=0.026. The significant effect of FP was confined to the moderate-to-severe group: FP median 1.47 exacerbations·yr^{-1}; placebo 1.75 exacerbations·yr^{-1}, $p<0.022$ (fig. 2). There was no statistically significant effect in the mild group (FP median 0.67 exacerbations·yr^{-1}; placebo 0.92 exacerbations·yr^{-1}, p=0.45). The frequency of exacerbations in the two patient groups remained unchanged throughout the 3 yrs of the study. In both treatment groups, neither the median rate nor the 'tail'

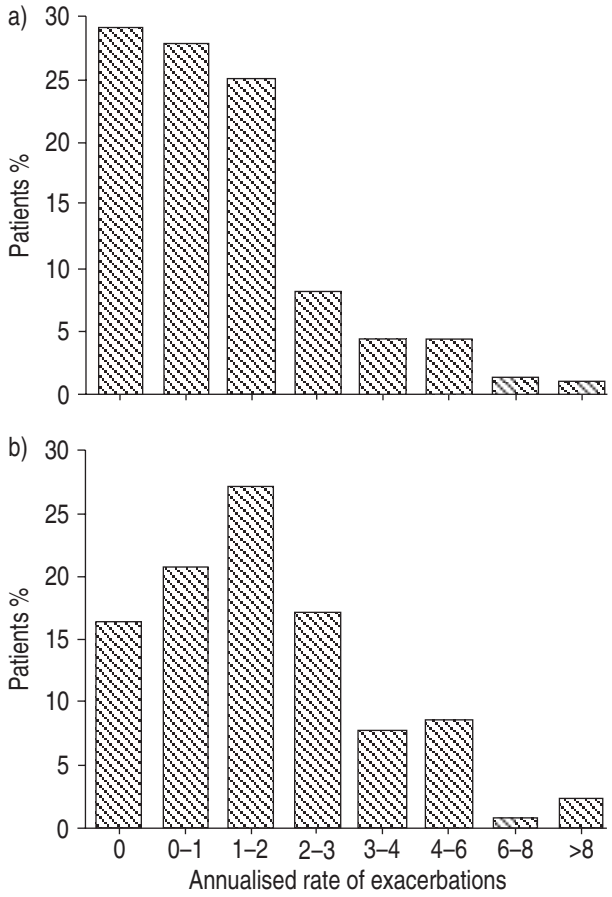

Fig. 1. – Frequency distribution for exacerbation rate per year in patients with a) mild and b) moderate-to-severe chronic obstructive pulmonary disease. In mild patients the distribution was highly skewed whereas in moderate-to-severe disease the distribution was more normally distributed.

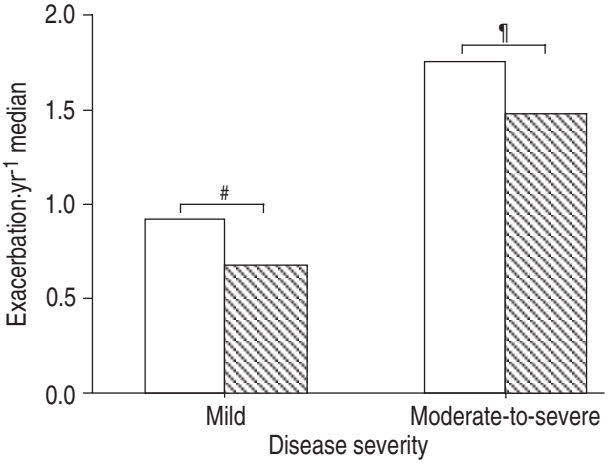

Fig. 2. – Bar chart of the median rate of exacerbations per year in placebo (□) and fluticasone propionate (▨) treated patients, split by disease severity (American Thoracic Society criteria). The Mann-Whitney rank-sum test was used to calculate p-values. #: p=0.45; ¶: p=0.022.

of patients with high numbers of exacerbations per year appeared to lessen.

Exacerbations treated with steroids

In patients with moderate-to-severe disease, 52% had a corticosteroid-treated exacerbation compared to 30% of the mild group (Fisher's exact test $p<0.0001$). The rate of these exacerbations was significantly lower in FP-treated patients compared to placebo, $p<0.001$. FP halved the number of patients having one or more exacerbations per year in both patient groups (fig. 3).

Reversibility and exacerbations

To test for the presence of subgroups of patients with a greater effect of inhaled corticosteroid, further

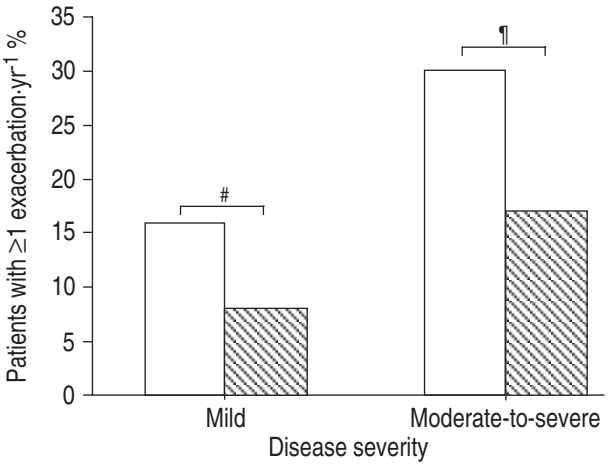

Fig. 3. – Bar chart of the percentage of patients having ≥ 1 corticosteroid-treated exacerbation·yr^{-1} in placebo (□) and fluticasone propionate (▨) treated patients, split by disease severity (American Thoracic Society criteria). The Mann-Whitney rank-sum test was used to calculate p-values. #: p=0.02; ¶: p=0.01.

post hoc analyses were carried out, dividing patients into those with greater or less reversibility to bronchodilator (median split cutting at 170 mL) and those with greater or less response to prednisolone (median split cutting at 50 mL). In none of these subgroups was the effect of fluticasone statistically significant ($p>0.05$ in each case).

Discussion

Reducing the number of exacerbations of COPD is an important goal of treatment and has been stressed in several treatment guidelines [4–6]. In patients treated with FP, the rate of exacerbations was reduced compared to the placebo-treated patients. This effect was confined to patients with more severe airflow limitation, since the difference between treatment groups was not statistically significant in the milder patients. This could represent a genuine difference in efficacy dependent on disease severity or be a reflection of the smaller number of episodes identified in mild disease and hence the risk of a Type 2 statistical error, since the proportional reduction was the same. Support for the latter view comes from the report of a beneficial effect of inhaled triamcinolone on emergency physician contacts in the recent large Lung Health Study II in patients with mild COPD [13].

Not all exacerbations were treated with oral steroids. Half of the patients with moderate-to-severe disease received at least one course compared with less than one third in those with mild disease. The reasons for this are not clear from the current study, but it is possible that doctors were more likely to prescribed oral steroids in patients with worse airflow limitation or those who appear to have more severe attacks. This conclusion is supported by data from a large Spanish community study in which prescription of oral corticosteroids was strongly related to the intensity of dyspnoea [18]. In both severity subgroups, FP halved the number of patients who needed one or more courses of oral corticosteroids in a year. In patients with moderate-to-severe disease it reduced the proportion of patients requiring oral corticosteroids to the level of those with mild disease treated with placebo.

The median exacerbation rate in the placebo-treated patients in this study was 1.3·patient^{-1}·yr^{-1}. This is similar to that in a large series of patients assessed for antibiotic treatment [19] and to the rate of 1.5·patient^{-1}·yr^{-1} reported in COPD patients with a similar disease severity in the UK [1]. The similarity in exacerbation rate between the latter study and the present study occurred despite two major differences between the studies. First, there were differences in definition of an exacerbation: increased cough and dyspnoea for ≥ 2 days used by SEEMUNGAL *et al.* [1] and chest problems requiring treatment with antibiotics and/or oral corticosteroids used in this study. Secondly, in the current study details of exacerbations were recorded retrospectively at 3-month intervals, whereas SEEMUNGAL *et al.* [1] collected their exacerbation data prospectively using diary cards. Furthermore, in the

current study there was also the potential to lose the effect of patients with the highest frequency of exacerbations because of the study criterion, which required withdrawal if three courses of oral steroids were needed in any 3-month period. However, this effect will have been small, since the tail of the frequency distribution curve of exacerbations contained only 9% of patients with an exacerbation rate >4 yr^{-1}, even in patients with moderate-to-severe COPD (fig. 1).

The frequency of exacerbations was significantly higher in patients with moderate-to-severe as compared to mild airflow limitation. Patients with mild disease had, on average, <1 exacerbation·yr^{-1} whereas those with moderate-to-severe disease had >1.5 exacerbations·yr^{-1}. Although the frequency distribution of the exacerbations was skewed towards relatively infrequent acute episodes, a quarter of moderate-to-severe patients still had >3 exacerbations·yr^{-1}. At the other end of the spectrum, during the entire 3-yr period, there were no acute episodes recorded in 16% of the moderate-to-severe patients who received placebo and 29% in those with mild disease. These data support the thresholds, based on FEV1, that are used in a number of treatment guidelines to identify patients at risk of greater morbidity [4].

The findings of the present study support earlier data in which, compared with placebo, FP significantly reduced the incidence of severe exacerbations, defined by the need for hospitalisation [8], however, FP had no effect on the time to first exacerbation. This may have been due in part to imprecision in the capture of the time of the first exacerbation, which in large measure depended on the patient's recall of the event when questioned at their 3-monthly visit. The total number of patients who experienced an exacerbation was also not influenced by FP. One interpretation of these observations is that the drug was having an effect in patients who were prone to recurrent exacerbations. This view is consistent with the finding that the treatment effect was most evident in patients with moderate-to-severe airflow limitation, who were also the group that had more frequent exacerbations and were more likely to be treated with courses of oral steroids in addition to antibiotics.

The parallel-group design of these placebo-controlled studies permits the conclusion that FP use was associated with a lower exacerbation frequency. The hypothesis that FP reduces exacerbation frequency can only be tested directly in a study in which patients act as their own controls and exacerbation frequency is measured before and after the introduction of the treatment. Such a study would require a crossover design and need either a very large number of patients or long duration in each arm to ensure adequate power. It is probably not practically possible to launch such a trial.

In conclusion, this analysis has shown that exacerbations are more frequent in patients with moderate-to-severe chronic obstructive pulmonary disease, a quarter of whom may require treatment with antibiotics and/or oral steroids three times in the course of a year. Fluticasone propionate significantly reduced both the rate of exacerbations in chronic obstructive pulmonary disease and the number of exacerbations treated with courses of oral corticosteroids. This effect was most apparent in patients with moderate-to-severe disease. Therefore, patients with moderate-to-severe chronic obstructive pulmonary disease and a history of recurrent exacerbations appear to be those most likely to benefit from this therapy, as proposed in the recent Global Initiative for Chronic Obstructive Lung Disease management guidelines [20].

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