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Stable COPD: predicting benefit from high dose inhaled corticosteroid treatment.

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Abstract

The role of inhaled corticosteroids in the management of chronic obstructive pulmonary disease (COPD) remains controversial. The purpose of this study was to evaluate whether sputum eosinophilia (≥3%) predicts clinical benefit from inhaled corticosteroid treatment in patients with stable moderate-severe smokers COPD.

Forty consecutive patients with effort dyspnoea (mean age 67 years; 52 pack-year smoking history; post-bronchodilator forced expiratory volume in one second (FEV_1) <60% predicted, consistent with moderate-severe smoking-related chronic airflow limitation) were enrolled. Subjects were treated with inhaled placebo followed by inhaled budesonide (Pulmicort Turbuhaler® 1600μg/day), each given for 4 weeks. While the treatment was single-blind (subject level), sputum cell counts before and after treatment interventions were double-blind, thus removing bias. Outcome variables included spirometry, quality of life assessment and 6-minute walk test.

Sputum eosinophilia was present in 38% of subjects. In these, budesonide treatment normalized the eosinophil counts and, in comparison to placebo treatment, resulted in clinically significant improvement in the dyspnoea domain of the disease specific chronic respiratory questionnaire (0.8 vs. 0.3) and a small but statistically significant improvement in post-bronchodilator spirometry (FEV_1 100 ml vs. 0 ml) ($p<0.05$).

We conclude that sputum eosinophilia predicts short-term clinical benefit from high dose inhaled corticosteroid treatment in patients with stable moderate-severe COPD.

Words: **204**

Keywords: COPD; airway inflammation; induced sputum; eosinophils; inhaled corticosteroids.

INTRODUCTION

The role of inhaled corticosteroids (ICS) in the management of stable chronic obstructive pulmonary disease (COPD) remains controversial (1, 2). The results of several large, multi-centre randomized controlled trials (3-7) suggest that there may be a small clinical benefit from ICS treatment, particularly in those patients with more severe disease. Nonetheless, despite the lack of compelling evidence for their use, many COPD patients are treated with regular ICS therapy (8). COPD is heterogeneous (9, 10), and there are likely to be sub-groups of patients who will benefit from ICS treatment. It is likely that such benefit within phenotypic sub-groups will be lost when the data from large randomized controlled trials are analyzed within a heterogeneous study population.

As yet, no useful predictor of clinical response to ICS treatment in patients with COPD has been identified (11, 12). We reasoned, based on previous studies showing that sputum eosinophilia predicts short-term clinical benefit from prednisone (or prednisolone) treatment in patients with COPD (13, 14), that sputum eosinophilia may also be a valid predictor of clinical benefit from ICS treatment. The purpose of this study was therefore to determine whether sputum eosinophilia (defined in this study as eosinophils ≥3%) is useful in predicting clinical benefit from treatment with high dose budesonide (800 μg twice daily), given for 4-weeks in patients with established, smoking related, clinically stable moderate-severe COPD.

METHODS

Subjects

Forty-four adults with a physician diagnosis of COPD (15) and the following characteristics were consecutively recruited from the respiratory clinics of three university centers. All subjects were 40 years or older, current or ex-smokers of 20 pack years or more, and had effort dyspnoea and moderate to severe COPD (GOLD stage II or III) as indicated by a post-bronchodilator FEV_1/slow vital capacity (SVC) of <70% and a post-bronchodilator forced expiratory volume in 1 second (FEV_1) <60% predicted. Partial post-bronchodilator airflow reversibility was not an exclusion criterion since the objective of the study was to investigate the predictive value of sputum eosinophilia. The subjects were stable on treatment with salbutamol or ipatropium; none had used either inhaled corticosteroid or prednisone for at least 2 months. The study was approved by the Research Ethics Boards of each study site, and all subjects gave written informed consent before participating in the study.

Study Design

This study was a three-centre, sequential placebo followed by budesonide treatment crossover trial. While the treatment was single-blind (subject level), bias was removed by double-blinding of induced sputum cell counts on which the analysis was based. There were five or six visits in the morning, within two-hours of visit one. At the first visit, subject characteristics were documented (including spirometry, quality of life, a 6-minute walk test and induced sputum examination) and subjects were instructed to continue their pre-study inhaled bronchodilator(s) as needed, and to record their use, plus symptoms on

a diary card. The walk test was repeated at a second and third visit, within a 7-day period to ensure its optimum performance. At visit three, spirometry and induced sputum examination was repeated and the subjects were started on inhaled placebo Turbuhaler®, 2 inhalations twice daily, for 4-weeks. At Visit 4 this treatment was changed to inhaled budesonide (Pulmicort Turbuhaler®) 400 μg, 2 inhalations twice daily (total daily dose 1600 μg) for a further 4-weeks. Finally at Visit 5, in those subjects who were agreeable, prednisone 30 mg daily was given for 14 days. Outcome measurements of pre- and post-bronchodilator FEV_1, quality of life assessment, 6-minute walk test and induced sputum cell counts were repeated at these visits and after prednisone treatment.

Methods

Treatment allocation was concealed from subjects for the duration of the study. The medications were supplied by AstraZeneca (AstraZeneca Inc., Mississauga, Canada) and were independently packaged and labelled by the hospital pharmacy. Placebo Turbuhalers® were identical in appearance and labelling to Pulmicort Turbuhaler®, so that patients were not able to determine treatment allocation. At the start of each treatment period, each subject was given a new coded Turbuhaler®; their inhalation technique was checked and corrected if necessary. At the end of each treatment period, study medication was returned and compliance was monitored by counting the number of remaining Turbuhaler® doses.

Subject characteristics were documented by questionnaire. Effort dyspnoea was assessed by the Medical Research Council dyspnoea scale (16). Allergy skin tests were performed by the modified prick technique (17) with common allergen extracts and a negative and positive control. Pre- and post-salbutamol (400 μg) FEV_1, SVC and

Inspiratory capacity (IC) were measured according to ATS specifications (18), after withholding inhaled beta-agonists or ipratropium bromide for at least six hours. Measurements obtained at visit 1 were recorded as baseline. Bronchodilator reversibility was considered to be present when the FEV_1 increased by 200 ml and >10% from predicted value (11). The quality of life assessment was measured by the disease specific Chronic Respiratory Questionnaire (CRQ) (19). For the Brazilian and French-Canadian centres, across-cultural adaptation of the questionnaire was developed and validated according to standard criteria (20). The CRQ measured four domains (dyspnoea, fatigue, emotion and mastery, using a 7-point Likert scale) and a global CRQ score was obtained from the sum of the four domains. The minimum change indicating a clinically important benefit was 2 points in global score and 0.5 points in each domain score. The 6-minute walk test was done according to a standardized protocol (21) at each of the first three visits to control for a possible learning effect; the longest distance walked on any of these visits was used as the baseline measurement (22). Sputum was induced with normal or hypertonic saline, was selected from expectorate and treated with dithiothreitol using the methods of Pizzichini, et al. (13, 23). It was examined for colour, cell viability with trypan blue, squamous cell contamination, total cell count in a hemocytometer, and differential cell count on Wright stained cytospins. Normal cell counts were taken from Belda et al (24). The cut point for normal eosinophils is ≤2% and that which usually indicates improvement with steroid treatment is ≥3% (13). Sputum cell counts performed at visit 1 and visit 2 were repeatable (intra-class correlation coefficient 0.9) and cell counts obtained at visit 2 were recorded as baseline. Quality assurance between study centers was assessed by inter-observer repeatability which was >0.9.

Analysis

In a previous study from our group (13), we confirmed that a sample size of 18 subjects with moderate-severe COPD was sufficiently powered to detect statistically significant differences in dyspnoea scores, quality of life and FEV_1 measurements following prednisone treatment in subjects with and without sputum eosinophilia. Using data from that study, we calculated *a priori* that a sample size of 40 subjects would provide sufficient power (≥80%) to detect a minimally important difference of 200 ml (SD 300 ml) in FEV_1 between the treatment groups in the present study.

Data were analyzed using SPSS for Windows, Release 10.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used to summarize the baseline characteristics of the study patients, and the results were expressed as arithmetic mean (SD) if the data were normally distributed, and as the median (IQR) if the data were non-normally distributed. Repeated measures ANOVA were used to test for the effects of treatment on the dependent variables, with post-hoc analysis used to identify the source of significant variation when present. All comparisons were two-tailed, and probability (p) values <0.05 were considered significant.

RESULTS

Of the 44 subjects enrolled in the study, four were excluded from the final analysis; two developed infective exacerbations during the study, one was non-compliant with treatment, and one died of an acute coronary thrombosis (confirmed at necropsy) during placebo treatment. The baseline characteristics of the remaining 40 subjects were stratified by sputum eosinophil counts (**Tables 1, 2**). Fifteen (38%) had sputum eosinophilia ≥3%, and these were more likely to be male and to have a greater degree of chronic airflow limitation compared to patients without sputum eosinophilia. There was no difference in other sputum characteristics between the two groups. Sputum eosinophilia did not predict the presence of atopy or of bronchodilator reversibility; sixteen (40%) subjects had bronchodilator reversibility >10% predicted and four (10%) >15% (**Figure 1**).

We examined the effects of budesonide treatment on sputum cell counts in the eosinophilic and non-eosinophilic groups (**Figure 2**). In all subjects with sputum eosinophilia, placebo treatment had no effect but budesonide reduced eosinophils into the normal range ($p<0.001$). In subjects with no eosinophilia, eosinophils remained in the normal range after both interventions (**Table 2)**. Budesonide treatment had no effect on other cell types in either group.

We examined the effects of budesonide treatment on clinical outcome variables. Budesonide produced a small but statistically significant increase in mean and absolute change in post-bronchodilator FEV_1 compared to placebo in subjects who had sputum eosinophilia (**Table 2, Figure 3**), as well as CRQ global and dyspnoea domain scores (**Table 2, Figures 4, 5**). The improvement in CRQ dyspnoea domain score was also

clinically relevant. Budesonide treatment did not result in any significant increase in the post-bronchodilator SVC or IC in the eosinophilic and non-eosinophilic groups. Also, budesonide did not increase the distance walked during the 6-minute walk test.

Thirty-four (85%) subjects (13 eosinophilic, 21 non-eosinophilic) agreed to participate in the prednisone arm of the study. Prednisone treatment resulted in further reduction of sputum eosinophils to <1% in both the eosinophilic ($p<0.001$ compared to baseline) and non-eosinophilic groups (**Figure 2**) and a small additional increase in CRQ global score (**Figures 3-5**). This now reached clinical relevance when compared to placebo treatment in subjects with sputum eosinophilia (**Figures 4, 5**). However, the beneficial effects of prednisone were not significantly greater than those achieved with budesonide.

We also examined the outcomes in all study participants without categorizing them into eosinophilic or non-eosinophilic sub-groups. Budesonide, and prednisone, resulted in a significant attenuation of sputum eosinophilia ($p<0.01$) when compared to placebo treatment, but neither treatment had any significant effect on CRQ or FEV_1 (Table 3).

DISCUSSION

In this study, treatment with inhaled budesonide 1600 μg/day for 4 weeks produced a clinically important and statistically significant effect on dyspnoea during day to day activities, and a small statistically significant improvement in post-bronchodilator FEV_1 in subjects who had sputum eosinophilia ≥3% compared to treatment with inhaled placebo. In contrast, subjects without sputum eosinophilia did not show benefit from inhaled budesonide treatment. These findings suggest that sputum cell counts are a useful measurement in the clinical management of COPD. They provide substantive evidence that sputum eosinophilia predicts clinical benefit from high-dose inhaled corticosteroid treatment.

The results are consistent with previous publications indicating that sputum eosinophilia is a predictor of clinical benefit from either prednisone or prednisolone treatment in patients with COPD (13, 14), and they extend this knowledge to treatment with high dose ICS. Sputum eosinophilia is relatively common finding in patients with clinically stable, moderate-severe, smoking-related COPD. It occurred in 38% of consecutively enrolled subjects in the present study, which is similar to the prevalence reported by others (13, 14 and 25) in similar cohorts of patients. The results differ from those recently reported by Brightling et al (25) in similar patients in a randomized double-blind crossover trial of inhaled mometasone 800 ug daily and placebo, each given for six weeks with a four-week washout period between treatments. The modest dose of mometasone was followed by a small but significant improvement in FEV_1, of 0.11 L only in those patients with sputum eosinophils of more than 3.9%. However, there was no improvement in CRQ or sputum eosinophils. The latter, when considered in relation to

the reduction of eosinophils seen in the present study, suggests that the dose of mometasone and its relative potency were too low to have optimal effects. While it would have been preferable to identify a predictive marker of ICS benefit that would be easier to measure than sputum eosinophilia, neither the presence of atopy alone (as defined by positive allergy skin prick tests), nor the presence of post-salbutamol reversibility alone, were able to predict clinical benefit to inhaled budesonide.

In considering the validity of these results we need to consider the characteristics of the subjects studied, the study design, sample size and the outcomes of CRQ and FEV_1. We did not exclude subjects with partial $\exists_2$-agonist bronchodilator reversible airflow limitation because it is recognized that a proportion of patients with COPD demonstrate significant post-bronchodilator reversibility (26) (i.e. by definition, they also have asthma). In elderly patients, with a significant smoking history and the presence of moderate-severe chronic airflow limitation, the primary clinical diagnosis is still likely to be that of smoking related COPD, regardless of whether or not there is an additional element of $\exists_2$-agonist reversible airflow limitation present. All the study participants in the current study were older than 40 years, all had a smoking history of >20 pack-years, the vast majority (>80%) were non-atopic on allergy skin testing, and they all had objective evidence of persistent chronic airflow limitation after salbutamol. There was no relationship between salbutamol reversibility and sputum eosinophilia, indicating that sputum eosinophilia is not necessarily characteristic of the asthma phenotype (27). We therefore believe that, from a clinical perspective, most physicians would label these patients as having smoking related COPD, regardless of whether or not there is also partial β_2-agonist bronchodilator reversibility. Thus, the results from our study are likely

to be broadly generalizable to other patients with clinically stable, physician diagnosed, COPD who are attending other outpatient clinics.

At the time we developed the study protocol, we reasoned that a parallel-group randomized controlled trial would require a substantially greater number of study subjects in order to complete the study and even then, as evidenced by a recent study by Humbert, et al. (28) there is no guarantee that randomization leads to matched study groups at baseline. We also carefully considered the merits of a randomized cross-over study design, but were cognizant of a number of potential methodological limitations that may be associated with such a design, including the uncertainty of the time needed for budesonide washout, which might have resulted in a treatment order effect. Thus, while we recognized the limitations of a single blind sequential order study design *a priori*, we considered that a single-blind design to be a methodologically acceptable approach to address this specific study question, particularly given that bias was removed by the sputum cell counts being performed in a double-blind fashion. We therefore decided to use a sequential, single blind cross over study design, rather than a randomized two-period crossover design, because of the increased possibility of the confounding influence of infective exacerbations, the uncertainty regarding the maximum washout period of high dose inhaled budesonide and the possibility of persistent clinical improvement beyond the active treatment period. The study was adequately powered to detect statistically significant differences in dyspnoea scores, quality of life and FEV_1 measurements between the treatment groups at, or below, thresholds of what are regarded as minimally important clinical differences.

The results of this study support previous observations that measurements of quality of life in severe COPD are more sensitive in detecting changes in functional status than FEV_1 (29-32). The dyspnoea domain of the CRQ seems to be more discriminatory than the global score and could be more easily applied in practice. O'Donnell (33) has drawn attention to the importance of hyperinflation in patients with advanced COPD and that, when there is subjective improvement with little or no change in FEV_1, there may be a reduction in hyperinflation identified by an increase in inspiratory capacity. We did not observe this in the present study. Neither did we record any improvement in the 6-minute walk test. A possible reason for the small FEV_1 improvement is that ICS cannot penetrate to more distal airways where much of the inflammation occurs. In this situation prednisone should be more effective. In the present study we assessed this by adding an optional third period of prednisone treatment; in patients with sputum eosinophilia, prednisone treatment was associated with a 7-fold reduction in sputum eosinophil counts, compared to budesonide treatment which was associated with only a 3-fold reduction in sputum eosinophil counts. This suggests that there may be a degree of inhaled steroid resistance in these patients, and the absence of apparent clinical benefit from a short burst of prednisone cannot necessarily be used to refute such an argument. Another reason for the small improvement in FEV_1 is that the clinical improvement resulted primarily from reduction of the inflammatory component as occurs in patients with eosinophilic bronchitis without asthma.

The present study assessed the short-term effects of inhaled corticosteroid treatment in patients with moderate-severe COPD. However, several large randomized controlled trials have demonstrated that ICS treatment is associated with a reduction in the number

of clinical exacerbations (5-7). Therefore, clinicians prescribing inhaled corticosteroids for patients with moderate-severe COPD are likely to do so with the expectation of preventing or reducing COPD exacerbations. In the context of our study, readers will be interested to note that the reduction in exacerbations seen with fluticasone in the ISOLDE study was largely confined to those subjects who had a good short-term response to corticosteroid treatment (34). Thus, it is possible that the presence of sputum eosinophilia may, in addition to predicting short-term benefits from inhaled corticosteroid treatment, also predict to longer-term benefits, including the reduction of exacerbations.

Patients with smoking-related chronic airflow limitation were eligible for entry into the study provided they had an FEV_1 <60% of predicted value; this cut-off was chosen as being the degree of physiological impairment at which patients with chronic airflow limitation might begin to experience symptoms of dyspneoa. As such, it was useful for us to identify such patients as being potentially suitable for our study. While the results from our study demonstrate clinical benefit from budesonide treatment in patients with moderate-severe COPD who have sputum eosinophilia, our study provides no justification to extend the current COPD guidelines, which recommend that inhaled corticosteroids in COPD only be initiated in patients when their FEV_1 <50% of predicted value.

The results of the current study are important, since current guidelines do not recognize a predictor for clinical benefit from ICS treatment in patients with COPD (11, 15, 35-37). They provide two potential reasons as to why previous large multi-centre trials in COPD have failed to convincingly show clinical benefit from inhaled steroid treatment (3-7). One reason is that they have failed to identify the subgroup of patients

with eosinophilic bronchitis who will benefit from corticosteroid treatment. If we had not done so in the present study, we would also have failed to identify improvement in CRQ or FEV1. The other reason for failure to show benefit in the multi-centre trials is that they may have used too low a dose of inhaled steroid. It may be that the results of our study under-estimate the true benefit of inhaled budesonide in patients with moderate-severe COPD. While we did not specifically discontinue inhaled corticosteroids in otherwise eligible patients in order to qualify them for the study, it is possible that patients who had previously benefited from a trial of inhaled corticosteroids were unlikely to have discontinued them, and thus they would not have been eligible for participation in our study.

While it is true that similar beneficial effects are seen in the great majority patients treated with inhaled long-acting anti-cholinergics or long-acting β-agonists, the use if these agents in COPD are well accepted, and form the cornerstone of pharmacological therapy as recommended by current COPD guidelines (11; 35-37). However, the guidelines are less clear in defining the role of ICS in COPD, perhaps in part because it is a heterogeneous condition, and there remains some debate as to which patients within this diagnostic group are likely to benefit significantly from the addition of ICS treatment. The aim of our study was to determine which phenotypes of patients with COPD are likely to benefit maximally from ICS therapy. We applied objective measurements of airway inflammation to identify those patients with COPD who should be identified as being likely to demonstrate a clinical response to ICS. Our data indicate that patients with clinically stable COPD who have sputum eosinophilia are the ones who should be treated with high-dose ICS, while those who do not have a sputum eosinophilia (approximately

60%) should not. Rather than promoting the widespread use of ICS in COPD, our data suggests that using sputum eosinophilia as a predictor of inhaled steroid responsiveness is a valid approach to justify healthcare utilization in COPD in an objective, evidenced-based approach.

Patients with sputum eosinophilia who showed clinical benefit to high-dose ICS were not necessarily those with frequent clinical exacerbations. In order to be eligible for entry into this study, patients needed to have been clinically stable for the preceding 8 weeks. Once randomized, the two study patients who experienced a clinical exacerbation during the 10 week study period were discontinued from the study and their data not included in the final analysis. The predictive benefit of budesonide in patients with sputum eosinophilia was nonetheless evident in patients who had been clinically stable for the 8 weeks prior to study entry, as well as for the 10-week duration of the study.

In summary, about one third of patients with clinically stable, moderate-severe smoking related COPD present with sputum eosinophilia. In the present study this was associated with a clinically important response to high-dose inhaled budesonide therapy as measured by effects on dyspnoea during day-to-day activities. This improvement in dyspnoea (which could be measured in practice by the CRQ dyspnoea domain) was associated with a small, but statistically significant improvement in FEV_1 (which may be easily missed in clinical practice) and in the global CRQ score. Improvements in these outcome variables were paralleled by a significant reduction in sputum eosinophil counts to the normal range in patients with sputum eosinophilia. We conclude that sputum eosinophilia predicts clinical benefit from inhaled high dose corticosteroid treatment in

patients with smoking related moderate-severe COPD, and that sputum cell counts are useful in the clinical management of these patients.

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FIGURE LEGENDS:

Figure 1

Scatter plot showing the relationship between sputum eosinophilia and response to inhaled salbutamol (expressed as a change in FEV_1 as a percentage of baseline, pre-bronchodilator FEV_1). Open circles represent patients with sputum eosinophils ≥3%; solid circles represent patients without sputum eosinophilia. Open and solid stars represent patients who are atopic in each group. Dashed vertical line represents upper limit of normal for sputum eosinophils and dashed horizontal line represents clinically important bronchodilator reversibility. Bronchodilator reversibility does not predict sputum eosinophilia.

Figure 2

Median percent sputum eosinophils in patients with (open circles) and without (solid circles) sputum eosinophilia ≥3% at baseline and after placebo, budesonide and prednisone treatment. Error bars represent Interquartile Range. * $p<0.001$ within group difference for budesonide and prednisone compared to placebo. Dashed line represents upper limit of normal sputum eosinophils. Eosinophilia is reversed by the budesonide treatment.

Figure 3

Change in post-bronchodilator (BD) FEV_1 (L) from baseline after placebo (Placebo), budesonide (Budesonide) and prednisone treatment (Prednisone). Hatched bars are patients with sputum eosinophilia ≥3% at baseline; solid bars are patients without sputum

eosinophilia. Error bars represent standard error of the mean. * $p<0.05$ for patients for within group (sputum eosinophilia) differences after budesonide and prednisone treatment compared to placebo. # $p<0.05$ for between group differences.

Figure 4

Change in global CRQ scores from baseline after placebo (Placebo), budesonide (Budesonide) and prednisone treatment (Prednisone). Hatched bars are patients with sputum eosinophilia ≥3% at baseline; solid bars are patients without sputum eosinophilia. Error bars represent standard error of the mean. * $p<0.05$ for within group (sputum eosinophilia) differences after budesonide and prednisone treatment compared to placebo. # $p<0.05$ for between group differences. Dashed line represents minimally important clinical difference.

Figure 5

Change in dyspnoea CRQ scores from baseline after placebo (Placebo), budesonide (Budesonide) and prednisone treatment (Prednisone). Hatched bars are patients with sputum eosinophilia ≥3% at baseline; solid bars are patients without sputum eosinophilia. Error bars represent standard error of the mean. ** $p<0.01$ for within group (sputum eosinophilia) differences after budesonide and prednisone treatment compared to placebo. # $p<0.05$ for between group differences. Dashed line represents minimally important clinical difference.

Table1. Baseline characteristics of subjects (n=40)

	Sputum eosinophils		
	≥ 3%	<3%	p
Subjects, n (%)	**15 (37.5)**	**25 (62.5)**	**NS**
Age, years (min-max)	**68 (55 - 78)**	**66 (41 – 86)**	**NS**
Male gender, n (%)	**13 (87)**	**13 (52)**	**0.04**
Smoking, pack years	**58 (27)**	**49 (24)**	**NS**
Atopic, n (%)	**2 (13.3)**	**5 (20)**	**0.4**
Post BD FEV_1, %	**41 (12)**	**56 (13)**	**0.001**
Post BD FEV_1/SlowVC %	**37 (8.8)**	**48 (9.6)**	**0.001**
Δ in FEV_1 after BD, % from predicted	**7.1 (4.2)**	**8.9 (4.2)**	**NS**
Δ in FEV_1 > 200 mL after BD, n (%)	**6 (40)**	**10 (40)**	**NS**

Data are expressed as mean and standard deviation unless otherwise specified. Atopic indicates one or more positive allergy skin prick tests. BD = bronchodilator. FEV_1 predicted values from Crapo et al (28) and are post-bronchodilator. NS = p>0.05.

Table 2. Changes in outcome variables in patients with and without sputum eosinophilia

	Sputum eosinophils

	≥3%				< 3%			
Treatment	Baseline	Post-placebo	Post-budesonide	Post-prednisone	Baseline	Post-placebo	Post-budesonide	Post-prednisone
Post BD FEV_1, L	1.1 (0.4)	1.1 (0.3)	1.2 (0.3)	1.2 (0.4)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)
Post BD SVC, L	3.3 (1.1)	3.4 (1.1)	3.6 (1.2)	3.6 (1.2)	3.2 (1.0)	3.2 (1.0)	3.2 (1.0)	3.2 (0.9)
CRQ global	17.9 (4.4)	17.9 (4.6)	19.6 (4.3)	20.6 (3.8)	17.2 (3.2)	18.3 (2.8)	19.2 (2.7)	20.8 (3.2)
CRQ dyspnea	3.9 (1.2)	3.9 (1.2)	4.7 (1.4)	4.7 (1.5)	3.6 (0.9)	3.9 (0.8)	4.2 (0.8)	4.3 (1.2)
6 minute walk distance, m	393 (135)	402 (132)	405 (136)	423 (75)	414 (77)	422 (83)	420 (91)	431 (118)
TCC x 10^6/ml	6.9 (17)	6.2 (5)	6.4 (14)	7.7 (10)	7.2 (15)	6.6 (8)	6.2 (6)	7.0 (5)
Sputum cell viability, %	82 (10)	81 (14)	76 (15)	83 (15)	80 (13)	80 (13)	78 (13)	85 (14)
Sputum eosinophils, % *	6.3 (4.0)	5.0 (7.8)	2.0 (2.9)	0.3 (1.3)	1.0 (11)	0.9 (1.4)	0.5 (0.6)	0.0 (1.6)
Sputum neutrophils, % *	76.3 (20)	59.0 (18)	72.7 (24)	76.8 (23)	67.0 (30)	69.4 (32)	62.6 (28)	78.5 (38)

Table 3. Changes in outcomes variables when assessed as a whole group

	All subjects			
Treatment	**Baseline**	**Post-placebo**	**Post-budesonide**	**Post-prednisone**
Post BD FEV_1, L	1.3 (0.4)	1.4 (0.4)	1.4 (0.5)	1.4 (0.4)
CRQ global	17.5 (3.6)	18.1 (3.5)	19.4 (3.4)	21.0 (3.4)
CRQ dyspnea	3.7 (1.0)	3.9 (0.9)	4.4 (1.1)	4.6 (1.3)
6 minute walk distance, m	406 (101)	414 (103)	414 (104)	430 (117)
Sputum eosinophils, %	1.9 (3.7)	1.6 (3.2)	0.8 (1.0)*	0.7 (1.4)*

Sputum eosinophils expressed as median and Interquartile Range (IQR). * $p < 0.05$.

Figure 1

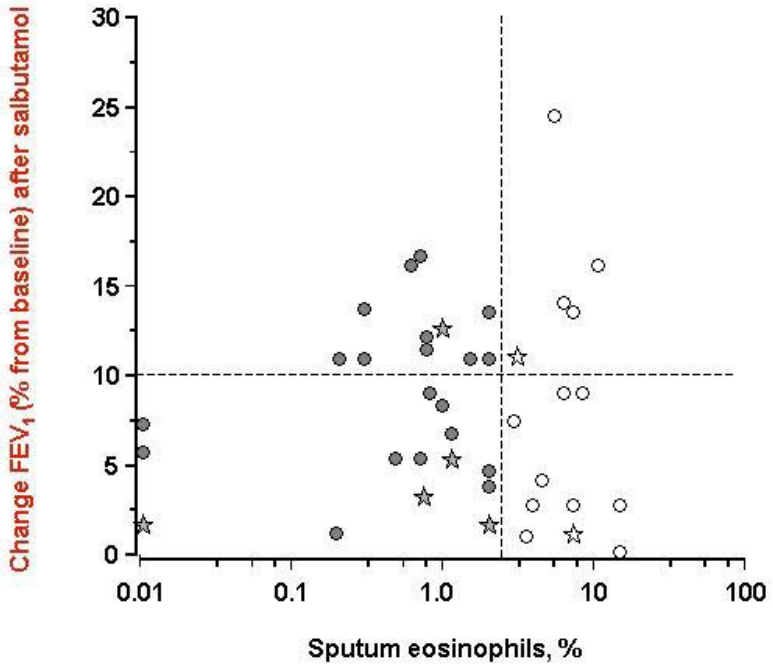

Change FEV1 (% from baseline) after salbutamol
30
25
20
15
10
5
0
0.01
0.1
1.0
10
100
Sputum eosinophils, %

Figure 2

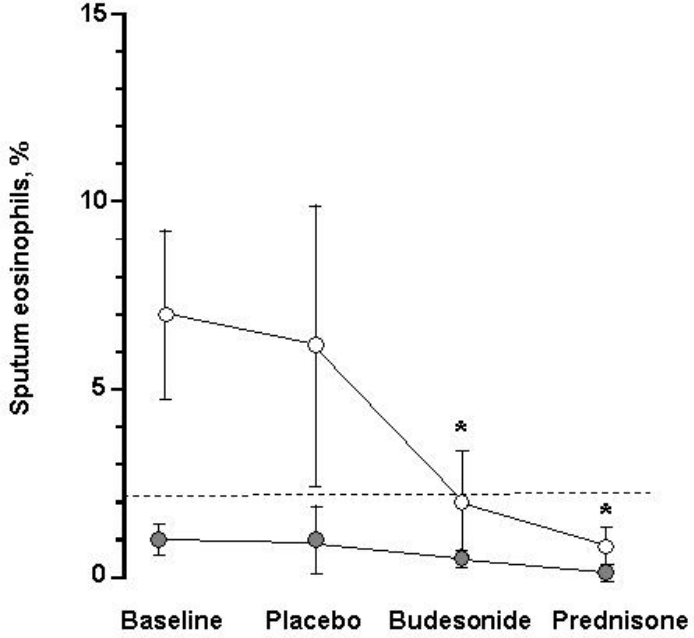

15
10
5
0
Sputum eosinophils, %
*
*
Baseline
Placebo
Budesonide
Prednisone

Figure 3

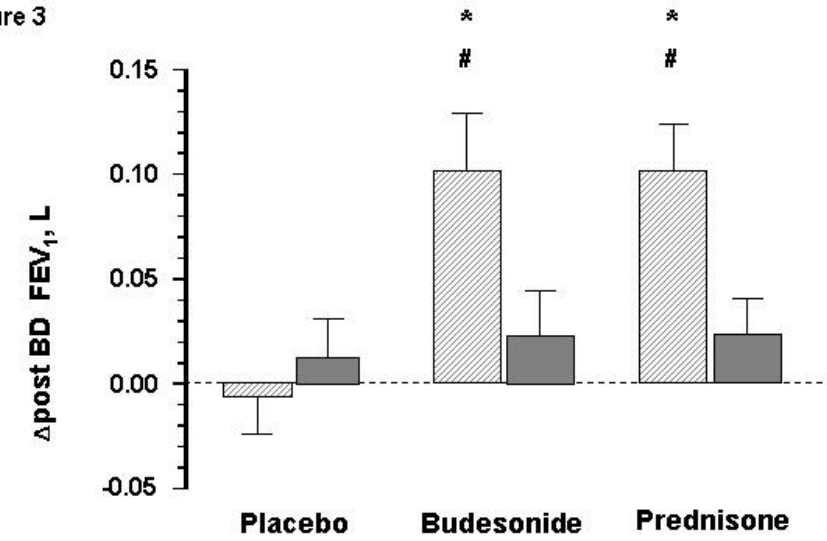

*
#
*
#
0.15
0.10
0.05
0.00
-0.05
Δpost BD FEV1, L
Placebo
Budesonide
Prednisone

Figure 4

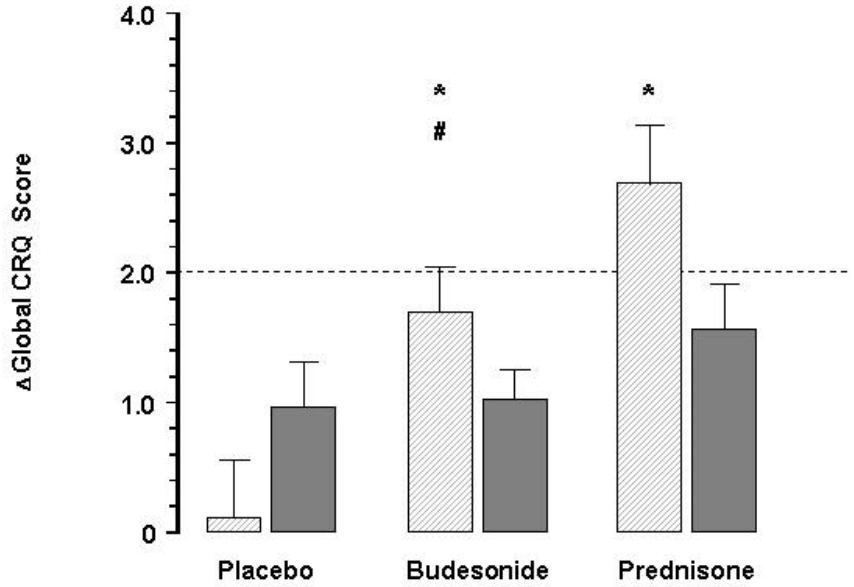
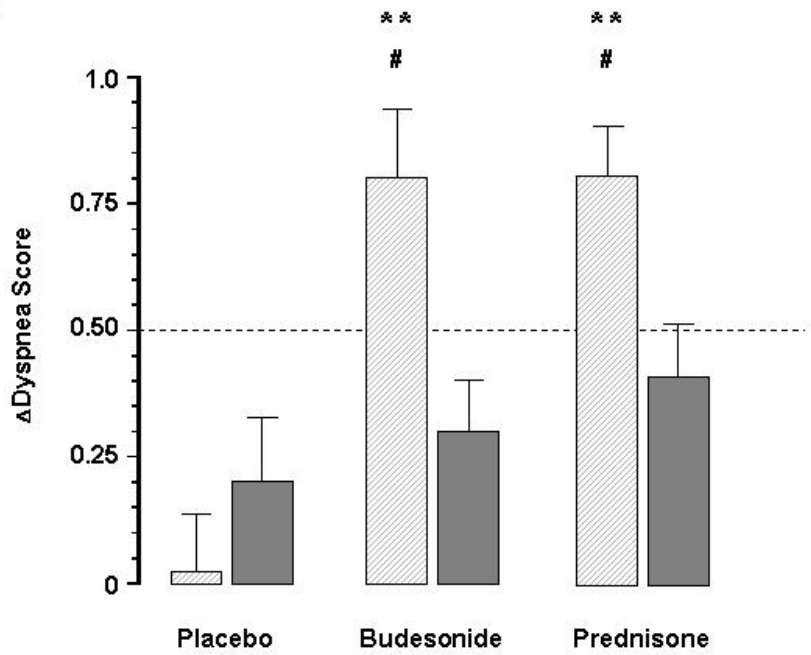

4.0
3.0
2.0
1.0
0
Δ Global CRQ Score
*
#
*
Placebo
Budesonide
Prednisone

Figure 5


**
#
**
#
1.0
0.75
0.50
0.25
0
ΔDyspnea Score
Placebo
Budesonide
Prednisone