

## CHRONIC OBSTRUCTIVE PULMONARY DISEASE

# Prednisolone response in patients with chronic obstructive pulmonary disease: results from the ISOLDE study

P S Burge, P M A Calverley, P W Jones, S Spencer, J A Anderson, on behalf of the ISOLDE Study Group

*Thorax* 2003;58:654–658

**Background:** A trial of corticosteroids has been recommended for all patients with chronic obstructive pulmonary disease (COPD), with the subsequent “response” determining the treatment selected. This approach assumes that patients can be reliably divided into responder and non-responder groups. We have assessed whether such a separation is statistically valid, which factors influence the change in forced expiratory volume in 1 second (FEV<sub>1</sub>) after prednisolone, and whether the prednisolone response predicts 3 year changes in FEV<sub>1</sub>, health status, or number of exacerbations during placebo or fluticasone propionate treatment.

**Methods:** Oral prednisolone 0.6 mg/kg was given for 14 days to 524 patients with COPD before randomised treatment for 3 years with fluticasone propionate or placebo. Factors relating to change in FEV<sub>1</sub> after prednisolone were investigated using multiple regression. The response to prednisolone was entered into separate mixed effects models of decline in FEV<sub>1</sub> and health status during the 3 years of the study.

**Results:** The post-bronchodilator FEV<sub>1</sub> increased by a mean 60 ml (CI 46 to 74) after prednisolone with a wide unimodal distribution. Current smoking was the factor most strongly associated with the change in FEV<sub>1</sub> after prednisolone, with an increase of 35 ml in current smokers and 74 ml in confirmed ex-smokers ( $p < 0.001$ ). There was no relationship between the change in FEV<sub>1</sub> after prednisolone and the response to inhaled bronchodilators, baseline FEV<sub>1</sub>, atopic status, age, or sex. The response to prednisolone, however expressed, was unrelated to the subsequent change in FEV<sub>1</sub> over the following 3 years on either placebo or fluticasone propionate. Regression to the mean effects explained much of the apparent prednisolone response. The significant effect of treatment on decline in health status was not predicted by the prednisolone response.

**Conclusion:** Patients with COPD cannot be separated into discrete groups of corticosteroid responders and non-responders. Current smoking reduces the FEV<sub>1</sub> response to prednisolone. Prednisolone testing is an unreliable predictor of the benefit from inhaled fluticasone propionate in individual patients.

See end of article for authors' affiliations

Correspondence to: Professor P S Burge, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK; sherwood.burge@heartsol.wmids.nhs.uk

Revised version received 8 January 2003  
Accepted for publication 20 February 2003

Chronic obstructive pulmonary disease (COPD) is progressive and leads to breathlessness, exacerbations, and often premature death. The disease is defined by airflow limitation “which does not change markedly over several months, and is due to variable combinations of airways disease and emphysema”.<sup>1</sup> In several countries a trial period of treatment with oral corticosteroids and measurement of the change in forced expiratory volume in 1 second (FEV<sub>1</sub>) is recommended to identify “responders who will be suitable for long-term inhaled therapy”,<sup>2</sup> and this approach is recommended for use in primary care in the UK.

In a meta-analysis of studies of short term oral corticosteroids, about 10% more subjects given corticosteroids had an improvement in FEV<sub>1</sub> from baseline of  $\geq 20\%$  than in placebo treated patients.<sup>3</sup> The separation of patients into corticosteroid responders and non-responders implies that the responders differ in some way from the non-responders, and that the separation is not due to chance. If the separation is real, the response to corticosteroids should not be normally distributed and should be reproducible. Moreover, responders and non-responders would be expected to respond differently to treatment with inhaled corticosteroids.

This study examines the distribution of the spirometric response to prednisolone in a well defined population of patients with non-asthmatic COPD, and its relationship with subsequent changes in FEV<sub>1</sub>, health status, and exacerbation rate over the following 3 years.

## METHODS

### Patients

Patients eligible for participation in the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study<sup>4</sup> had a clinical diagnosis of non-asthmatic COPD, were aged 40–75 years, and had a history of current or previous smoking. At baseline, post-bronchodilator (400 µg salbutamol) FEV<sub>1</sub> was  $\geq 0.8$  l and  $< 85\%$  predicted,<sup>5</sup> and the ratio of FEV<sub>1</sub> to forced vital capacity (FVC) was  $< 70\%$ . The FEV<sub>1</sub> response to salbutamol was  $< 10\%$  predicted. Patients with a clinical diagnosis of asthma, those requiring any non-trial anti-inflammatory treatment for lung disease or  $\beta$  adrenergic blockers, patients with a life expectancy  $< 5$  years, and those unable to meet the required standards for spirometry at the pre-trial visit were excluded. Nasal and ocular topical corticosteroids were allowed, as were methylxanthines and long acting bronchodilators. All patients were given salbutamol 200 µg and ipratropium bromide 80 µg to use as required throughout the trial.

### Study design

Full details of the study design have been published elsewhere.<sup>4</sup> Patients entered a run-in period of 8 weeks when no oral or inhaled corticosteroids were taken. Those included in the ISOLDE trial were then randomised in a double blind manner to treatment with fluticasone propionate 500 µg twice daily or matched placebo for 3 years, but were given prednisolone 0.6 mg/kg for 14 days before starting the randomised treatments.<sup>4</sup> Spirometric testing was performed

**Table 1** Baseline characteristics

	Patients completing oral steroid trial and providing valid data (N=524)
Mean (SD) age	64.0 (7.0)
Male, N (%)	407 (78%)
Atopic, N (%) (missing = 7)	143 (28%)
Current smoker, N (%)	246 (47%)
Ex-smoker, N (%)	278 (53%)
Mean (SD) smoking (pack years) (missing = 38)	44.6 (31.7)
Mean (SD) FEV <sub>1</sub> pre-bronchodilator (l)	1.23 (0.45)
Mean (SD) FEV <sub>1</sub> pre-bronchodilator (% predicted)	43.1 (14.5)
Mean (SD) FEV <sub>1</sub> post-bronchodilator (l)	1.40 (0.48)
Mean (SD) FEV <sub>1</sub> post-bronchodilator (% predicted)	49.3 (14.6)
Mean (SD) ΔFEV <sub>1</sub> post – pre-bronchodilator (ml)	179 (128)
Mean (SD) FVC post-bronchodilator (l)	3.32 (0.78)
Mean (SD) FVC post-bronchodilator (% predicted)	92.0 (16.3)
Mean (SD) TlCO (% predicted) (missing = 76)	56.4 (24.4)

FEV<sub>1</sub>=forced expiratory volume in 1 second; FVC=forced vital capacity; TlCO=carbon monoxide transfer factor.

at enrollment (visit 0), after 4 weeks (visit 1), after 8 weeks (visit 2), and again after the 2 week prednisolone trial (visit 3).

The protocol was approved by the ethics committee of each participating centre and all subjects gave written informed consent.

#### Baseline measurements

Smoking history was validated using exhaled breath carbon monoxide and urinary cotinine measurements. Smokers were defined as those currently smoking or with a urinary cotinine level of  $\geq 40$  ng/ml. Ex-smokers were those who had given up smoking and had a urinary cotinine level of  $< 40$  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 minutes. Maximum wheal diameters were measured and atopy was defined as a  $\geq 3$  mm wheal to at least one allergen extract with appropriate controls. Health status was measured using the St George's Respiratory Questionnaire (SGRQ).<sup>6</sup>

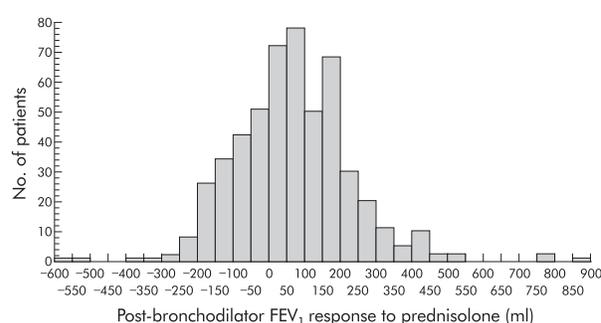
#### Spirometric measurements (FEV<sub>1</sub> and FVC)

Measurements were made at the same time of day for each subject after withholding short acting bronchodilators for 4 hours, oral or long acting bronchodilators for 12 hours, caffeine containing products for 4 hours, smoking for 2 hours, and large meals for 1 hour. Measurements were made seated after 15 minutes resting. The spirometric tests were performed pre-bronchodilator and 30 minutes after taking 80  $\mu$ g ipratropium bromide and 200  $\mu$ g salbutamol.<sup>4</sup>

An exacerbation was defined as a chest problem requiring treatment with oral corticosteroids and/or antibiotics as defined by the treating physician. Two 14 day exacerbations were permitted in any 3 month period; patients were withdrawn (as a respiratory withdrawal) if exacerbations exceeded this. At each clinic visit the number of exacerbations in the previous 3 months was recorded. Exacerbations were calculated as the rate per day in the trial per year.

#### Statistical methods

To investigate the factors associated with the 2 week prednisolone trial response, the change in post-bronchodilator FEV<sub>1</sub> before and after prednisolone (visit 3 – visit 2) was used as the dependent variable in a multivariate analysis using the generalised linear models procedure in SAS. Independent variables were baseline smoking status (current or ex-smokers), age, post-bronchodilator FEV<sub>1</sub> (visit 1), FEV<sub>1</sub> revers-



**Figure 1** Distribution of changes in post-bronchodilator FEV<sub>1</sub> following prednisolone.

ibility after salbutamol and ipratropium bromide (visit 0), sex, and atopy (yes or no).

Callahan and colleagues<sup>3</sup> defined steroid responders as patients with a response to prednisolone of  $\geq 20\%$  of baseline. The American Thoracic Society (ATS) defines responders as those with a response of  $> 12\%$  baseline and  $> 200$  ml. These were termed the Callahan and ATS criteria, respectively, and were used to determine differences between steroid responders and non-responders.

The relationships between the prednisolone response and the change in FEV<sub>1</sub> and health status in the 3 year comparison of fluticasone propionate and placebo were investigated by including the FEV<sub>1</sub> post-bronchodilator response to prednisolone as a covariate in the mixed effects models described in previous publications.<sup>4,7</sup> The number of exacerbations occurring during the treatment period was analysed using a maximum likelihood based analysis, assuming the Poisson distribution, with time on treatment as an offset variable, using the SAS GENMOD procedure for fitting generalised linear models. The model included terms for age, sex, centre, smoking status, treatment, responder classification, and the treatment  $\times$  responder classification interaction.

#### RESULTS

The results are confined to the 524 subjects who had taken at least 80% of the prednisolone treatment and had FEV<sub>1</sub> readings unaffected by respiratory exacerbations. Baseline characteristics of this group are shown in table 1. A further 47 patients stated that they had taken less than 80% of the prescribed prednisolone dose and 77 were excluded because of exacerbations within 4 weeks of the pre- or post-prednisolone visits; these 124 patients were not included in the analyses.

**Table 2** Relationship between variability in FEV<sub>1</sub> and prednisolone response

Change in FEV <sub>1</sub>	Prednisolone response		
	<-20%	-20% to +20%	>+20%
N	8	447	59
Visit 1 – Visit 0	-67 ml (158 ml)	-50 ml (155 ml)	-107 ml (168 ml)
Visit 2 – Visit 1	47 ml (105 ml)	-10 ml (132 ml)	-127 ml (187 ml)

**Table 3** Characteristics of smokers and confirmed ex-smokers who received prednisolone

	Ex-smokers (n=278)	Smokers (n=246)	p value
Male (%)	81.7	73.2	0.02
Atopic (%)	31.0	24.0	0.09
Age	65.8 (6.2)	61.9 (7.2)	<0.001
FEV <sub>1</sub> pre-bronchodilator (l)	1.18 (0.44)	1.27 (0.46)	0.030
FEV <sub>1</sub> pre-bronchodilator (% predicted)	41.7 (14.9)	44.7 (13.8)	0.019
FEV <sub>1</sub> post-bronchodilator (l)	1.36 (0.46)	1.45 (0.49)	0.042
FEV <sub>1</sub> post-bronchodilator (% predicted)	48.0 (15.0)	50.8 (14.1)	0.025
ΔFEV <sub>1</sub> post-bronchodilator	180 (125)	178 (131)	0.897
FVC pre-bronchodilator (l)	2.93 (0.69)	2.98 (0.82)	0.428
FVC pre-bronchodilator (% predicted)	80.8 (17.8)	83.1 (16.9)	0.138
FVC post-bronchodilator (l)	3.31 (0.69)	3.34 (0.86)	0.637
FVC post-bronchodilator (% predicted)	91.1 (16.4)	92.9 (16.2)	0.205
Change in FEV <sub>1</sub> (ml) following prednisolone (mean (SE) from multivariate model)	74 (12)	35 (11)	<0.01

Values are mean (SD) unless otherwise indicated.  
FEV<sub>1</sub>=forced expiratory volume in 1 second; FVC=forced vital capacity.

103 subjects either elected not to participate in the oral steroid trial or declined on medical advice. The baseline characteristics of these 227 patients did not differ from the 524 patients included in this study.

#### Response to 14 day course of oral steroids

The mean pre-bronchodilator FEV<sub>1</sub> response to prednisolone was 69 ml (95% CI 53 to 85) and the mean post-bronchodilator response was 60 ml (95% CI 46 to 74). Figure 1 shows that post-bronchodilator responses were broadly distributed around the mean value. The post-bronchodilator response was distributed across a narrower range of values than the pre-bronchodilator response.

#### Separation of corticosteroid “responders” from “non-responders”

The post-bronchodilator FEV<sub>1</sub> response to prednisolone (fig 1) was unimodally distributed, which suggests that the definition of “responders” and “non-responders” is arbitrary. According to the Callahan definition, 62 patients were responders with a mean (SD) post-bronchodilator change of 329 (145) ml and 462 were non-responders with a mean (SD) change of 25 (127) ml. According to the ATS definition, 74 responders had a mean (SD) change of 324 (130) ml and 450 non-responders had a change of 17 (121) ml. Responders and non-responders were not significantly different at baseline in terms of age, atopy, sex, and pack years of smoking ( $p>0.05$ ).

#### Effects of between visit FEV<sub>1</sub> variability on prednisolone response

Table 2 shows the change in post-bronchodilator FEV<sub>1</sub> between measurements taken during the run-in phase by prednisolone response category. In the 4 weeks immediately preceding the prednisolone trial, the mean (SD) FEV<sub>1</sub> fell significantly more in the responder group (-127 (187) ml) than in the intermediate group (-10 (132) ml) and the group who deteriorated after prednisolone (+47 (105) ml). Patients with a post-bronchodilator FEV<sub>1</sub> response to prednisolone of >20% of baseline had a significantly greater fall in FEV<sub>1</sub> during the

run-in phase than those with a lower or negative response to prednisolone ( $p<0.01$ ). There was no significant difference in prednisolone response between steroid naïve patients (48 ml,  $n=236$ ) and those withdrawn from inhaled steroids at least 8 weeks previously (71 ml,  $n=238$ ,  $p=0.1$ ).

#### Factors relating to FEV<sub>1</sub> post-bronchodilator response to prednisolone

A multivariate analysis showed that age, atopy, sex, baseline FEV<sub>1</sub>, and bronchodilator response were not significantly related to the response to prednisolone ( $p>0.05$ ). However, the FEV<sub>1</sub> response to prednisolone was greater in ex-smokers (mean (SE) 74(12) ml) than in smokers (mean (SE) 35 (11) ml;  $p<0.01$ ). The characteristics of the population of smokers and ex-smokers are shown in table 3. Smokers were 4 years younger than the ex-smokers and differences in FEV<sub>1</sub> indicated that they also had better lung function. The model also gave the following estimates for the prednisolone response: atopics 48 ml, non-atopics 65 ml; men 54 ml, women 55 ml.

#### Relationship between prednisolone response and FEV<sub>1</sub> change over 3 years

There was no significant relationship between the response to prednisolone and the subsequent decline in FEV<sub>1</sub>, regardless of response definition or treatment subgroup (table 4; analysis of variance  $p>0.1$  for all comparisons and interactions). However, when the response to prednisolone was fitted as a continuous explanatory variable there was a marginally significant interaction ( $p=0.056$ ) between this and the treatment main effect. A typical patient with a 14 day response to prednisolone of 50 ml would be predicted to obtain an additional immediate benefit of 8 ml on fluticasone but no difference in the subsequent FEV<sub>1</sub> decline compared with a patient with no response to prednisolone. However, as this benefit is so small, even if it assumed that the interaction is real, it is of no clinical relevance. Similarly, it did not predict the rate of deterioration in health status as measured by the SGRQ Total score ( $p=0.1$ ).

**Table 4** Modelled decline in FEV<sub>1</sub> related to responder definition and treatment group

	Fluticasone propionate		Placebo	
	n	ΔFEV <sub>1</sub> , ml/year (95% CI)	n	ΔFEV <sub>1</sub> , ml/year (95% CI)
Callahan responder	29	50 (20 to 80)	24	64 (33 to 96)
Callahan non-responder	213	47 (37 to 57)	206	55 (45 to 66)
ATS responder	36	55 (29 to 80)	30	67 (40 to 95)
ATS non-responder	206	46 (36 to 56)	200	55 (44 to 66)

**Table 5** Relationship between number of exacerbations per year and prednisolone response using the Callahan and ATS definitions

	Fluticasone propionate		Placebo		% reduction (95% CI)
	n	Mean*	n	Mean*	
Callahan responder	29	0.85	33	1.90	55% (25 to 74)
Callahan non-responder	232	1.32	229	1.55	15% (0 to 28)
ATS responder	37	1.10	37	1.68	35% (0 to 58)
ATS non-responder	224	1.39	225	1.57	17% (2 to 30)

\*Mean number of exacerbations per year from Poisson model.

### Relationship between prednisolone response and exacerbation rate

A Poisson analysis was performed to relate the number of exacerbations to treatment, prednisolone response using the ATS or Callahan definition, and any interaction. When the patients were subdivided using the ATS definition, fluticasone reduced the number of exacerbations by an average of 20% (95% CI 6 to 21;  $p=0.006$ ), but there was no evidence that the prednisolone response as defined by the ATS was an indicator of the effect of fluticasone ( $p=0.301$  for the treatment by ATS responder interaction). Using the Callahan definition, the effect of fluticasone on the responders was a 55% reduction in the number of exacerbations, while the effect on the non-responders was 15%. This difference in effect was statistically significant ( $p=0.018$ , table 5).

### DISCUSSION

This is the largest group of patients with COPD studied in a formal corticosteroid trial and, in particular, with carefully controlled and audited spirometric tests performed at the same time of day. The patients were similar to those in whom a "trial of steroids" is generally recommended, being at the stage of their disease where medical attention had been sought.<sup>2</sup> The changes in post-bronchodilator FEV<sub>1</sub> after prednisolone were unimodally distributed about the mean with no evidence of a separable responder group. Substitution of pre-bronchodilator values as used in normal clinical practice did not change the results. The patients were not randomised to prednisolone or placebo, so the changes seen after prednisolone cannot categorically be attributed to this drug. However, the data here are a reasonable reflection of those likely to appear in clinical practice. Crossover trials of prednisolone versus placebo have shown a carry-over effect from prednisolone to placebo of up to 6 weeks.<sup>8</sup>

Our patients were recruited because they had a clinical diagnosis of COPD, a history of tobacco smoking, and a bronchodilator response of <10% of predicted. Despite this, the distribution of response to prednisolone is wide; 95% of the ex-smokers had an FEV<sub>1</sub> response of 412 ml or less, suggesting that changes would need to be greater than this before an alternative diagnosis could be made with any confidence. Whether individuals who exceed these values have

bronchial asthma is unlikely to be resolved without pathological studies. Atopy is the most important identifiable risk factor for the development of asthma.<sup>9</sup> We found no significant differences in the spirometric response to prednisolone between atopic and non-atopic patients, making it unlikely that our population contained enough "hidden asthmatics" to influence the overall conclusions.

There was evidence of a significant regression to the mean effect even using post-bronchodilator FEV<sub>1</sub> as the outcome measure. Patients who had the greatest fall in FEV<sub>1</sub> following prednisolone showed the greatest increase before the prednisolone trial. Similarly, patients whose FEV<sub>1</sub> increased most after prednisolone were those who had the greatest deterioration in the 4 weeks before the trial. In an individual patient this change could be sufficiently large to suggest a clinically important benefit when none was present. This makes it difficult to define a subgroup of patients with COPD who are likely to "respond" but, despite this, several attempts to define responder groups have been made.<sup>10-11</sup> Factors influenced by variability in spirometry, such as bronchodilator response and diurnal variation in peak expiratory flow, have generally been included. In our carefully defined population we found no relationship with the bronchodilator response. Only one study has developed a discriminant function based on these variables which has been applied to a separate population prospectively and was found to be non-discriminatory.<sup>12</sup> This supports the lack of a true differentiation between steroid responders and non-responders. Women appear particularly prone to COPD when exposed to similar amounts of tobacco,<sup>13</sup> but we found no sex differences in prednisolone responsiveness. Continued smoking reduces the benefits of inhaled corticosteroids in asthma.<sup>14</sup> Our data suggest that in COPD this is also true during short term treatment with oral corticosteroids.

Corticosteroid trials are advocated as a method of selecting those patients with COPD who might benefit from long term corticosteroid treatment. We found no relationship between the short term response to prednisolone and the rate of decline in FEV<sub>1</sub> or health status. The only other study that investigated this relationship similarly found no difference (corticosteroid responders 35 ml/year, non-responders 29 ml/year while taking inhaled beclomethasone dipropionate).<sup>15</sup> Our data emphasise that the change in lung function after

corticosteroids is normally distributed and modified by smoking status. Studies in large patient groups permit the detection of these effects, but the small signal and relatively large day to day variation in lung function make its accurate detection in routine clinical practice extremely difficult.

A reduction in exacerbation frequency was one of the main results of the ISOLDE study. We investigated whether this benefit could be predicted by the steroid trial. There was no relationship with steroid response using the ATS definition which requires a minimum change in FEV<sub>1</sub> of 200 ml, overcoming the confounding effects of a low denominator and FEV<sub>1</sub> response which can occur using the Callahan definition. As a low FEV<sub>1</sub> is associated with a greater exacerbation reduction with inhaled fluticasone use in this study, and is associated both with exacerbation frequency and a Callahan response, we believe that the results seen using the Callahan criteria were confounded by these relationships. This is supported by our evidence that differences in the response to prednisolone are largely due to a regression to the mean effect, rather than a real difference between subjects.

In conclusion, undertaking corticosteroid trials in patients like these, especially in primary care, is not likely to be helpful diagnostically and can be misleading unless the increase in FEV<sub>1</sub> following prednisolone is more than 412 ml when an alternative diagnosis could be considered.

#### ACKNOWLEDGEMENTS

Significant contributions in recruiting patients and with data collection were provided by: Professor J G Ayres, Mrs G Bale, Professor N Barnes, Mrs C Baveystock, Dr G F A Benfield, Ms K Bentley, Dr Birenacki, Ms G Boar, Dr P Bright, Ms M Campbell, Ms P Carpenter, Ms S Cattell, Dr I I Coutts, Dr L Davies, Ms C Dawe, Ms J Dowselt, Ms K Dwyer, Mrs C Evans, Ms N Fasey, Dr A G Fennerty, Dr D Fishwick, Ms H Francis, Dr T Frank, Mrs D Frost, Professor G J Gibson, Dr J Hadcroft, Dr M G Halpin, Mrs O Harvey, Dr P Howard, Dr N A Jarad, Ms J Jones, Dr K Lewis, Mrs F Marsh, Mrs N Martin, Dr M D L Morgan, Ms L Morgan, Mrs W McDonald, Ms T Melody, Dr R D H Monie, Dr M F Muers, Dr R Niven, Dr C O'Brien, Ms V O'Dwyer, Ms S Parker, Dr M Peake, Dr W H Perks, Professor C A C Pickering, Dr J C Pounsford, Mrs K Pye, Mr G Rees, Ms A Reid, Ms K Roberts, Mrs C Robertson, Dr R M Rudd, Ms S Rudkin, Mr S Scholey, Dr P Scott, Dr T Seemungal, Ms S Shaldon, Dr C D Sheldon, Ms T Small, Professor S G Spiro, Dr J R Stradling, Ms H Talbot, Mrs J Waterhouse, Mrs L Webber, Professor J A Wedzicha, Ms M J Wild. Significant input into the design of the study was also provided by Dr D Weir.

#### Authors' affiliations

**P S Burge**, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK  
**P M A Calverley**, University Hospital Aintree, Liverpool L9 7AL, UK  
**P W Jones, S Spencer**, St George's Hospital Medical School, London SW17 0RE, UK  
**J A Anderson**, GlaxoWellcome Research and Development, Stockley Park West, Middlesex, UK

The ISOLDE study was funded by GlaxoWellcome Research and Development.

#### REFERENCES

- 1 **Siafakas NM**, Vermeire P, Pride NB, *et al*. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995;**8**:1398-420.
- 2 **British Thoracic Society**. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;**52**(Suppl 5):S1-28.
- 3 **Callahan CM**, Dittus RS, Katz BP. Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease. A meta-analysis. *Ann Intern Med* 1991;**114**:216-23.
- 4 **Burge PS**, Calverley PMA, Jones PW, *et al*. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;**320**:1297-303.
- 5 **Anonymous**. Standardized lung function testing. Report of working party. *Bull Eur Physiopathol Respir* 1983;**19**(Suppl):1-95.
- 6 **Jones PW**, Quirk FH, Baveystock CM, *et al*. A self-completed measure of health status for chronic airflow limitation. The St George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;**145**:1321-7.
- 7 **Goldstein H**. *Multilevel statistical models*. 2nd ed. London: Edward Arnold, 1995.
- 8 **Weir DC**, Gove RI, Robertson AS, *et al*. Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate. *Thorax* 1990;**45**:112-7.
- 9 **Sunyer J**, Anto JM, Kogevinas M, *et al*. Risk factors for asthma in young adults. Spanish group of the European Community Respiratory Health Survey. *Eur Respir J* 1997;**10**:2490-4.
- 10 **Weir DC**, Gove RI, Robertson AS, *et al*. Response to corticosteroids in chronic airflow obstruction: relationship to emphysema and airways collapse. *Eur Respir J* 1991;**4**:1185-90.
- 11 **Lam WK**, So SY, Yu DY. Response to oral corticosteroids in chronic airflow obstruction. *Br J Dis Chest* 1983;**77**:189-98.
- 12 **Weir DC**, Burge PS. Prediction of acute response to corticosteroids in patients with chronic airflow obstruction. *Eur Respir J* 1995;**8**(Suppl 19):166s.
- 13 **Prescott E**, Bjerg AM, Andersen PK, *et al*. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997;**10**:822-7.
- 14 **Pedersen B**, Dahl R, Karlstrom R, *et al*. Eosinophil and neutrophil activity in asthma in a one-year trial with inhaled budesonide. The impact of smoking. *Am J Respir Crit Care Med* 1996;**153**:1519-29.
- 15 **Weir DC**, Weiland GA, Burge PS. Decline in FEV<sub>1</sub> in patients with chronic airflow obstruction. Relation to acute steroid response and treatment with inhaled corticosteroids. In: Postma DS, Gerritsen J, eds. *Bronchitis V*. Assen: Van Gorcum, 1994: 280-6.