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Airways hyperresponsiveness, bronchodilator response, allergy and smoking predict improvement in FEV_1 during long-term inhaled corticosteroid treatment

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ABSTRACT: Although most patients with obstructive airways disease show some amelioration with long-term inhaled corticosteroid therapy, the extent of improvement may vary considerably between patients.

Patients with mild to moderately severe obstructive airways disease (asthma and COPD) were selected if provocative concentration producing a 20% fall in forced expiratory volume in one second (PC_{20}) ≤8 mg·ml^{-1}, and forced expiratory volume in one second (FEV_1) <95% confidence intervals (CI) of predicted normal. The independent influences of baseline $PC_{20}FEV_1$, inspiratory vital capacity (IVC), bronchodilator response, smoking habits, and allergy both on the "immediate" (within 3 months) response in FEV_1 and the change in long-term (from 3 months onwards) slope of FEV_1 with inhaled corticosteroids were analysed.

Patients had a larger "immediate" improvement in their FEV_1 with inhaled corticosteroids with each doubling doses lower PC_{20}, with each ten-fold higher immunoglobulin E (IgE), and if they did not smoke. Total IgE proved a better independent predictor of "immediate" response than specific IgE for house dust mite, skin tests, or blood eosinophils. A more favourable long-term slope of FEV_1 was predicted by a larger baseline bronchodilator response, but not by smoking.

In conclusion, PC_{20}, total IgE, and smoking habits are independent predictors of immediate treatment response to inhaled corticosteroids. Bronchodilator response is the single independent predictor of changes in long-term slope of FEV_1 with corticosteroid treatment.

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Inhaled corticosteroids have been used in the treatment of obstructive airways disease (asthma and chronic obstructive pulmonary disease (COPD)) since their introduction 20 yrs ago [1]. They have proved to be effective in long-term management of asthma [2–5]. Also, a beneficial effect has been suggested in COPD [5, 6], and is still under study (European Respiratory Society Study on Chronic Obstructive Pulmonary Disease [7]).

Many patients with obstructive airways disease show improvement in forced expiratory volume in one second (FEV_1) with inhaled corticosteroid therapy, but the extent of the improvement varies considerably between patients and studies [2, 4, 5, 8–11]. There are, however, only a few studies that report an attempt to predict the response to inhaled corticosteroids from baseline patient characteristics: no prognostic factors could be identified in asthma [2, 4], or in COPD [9–11], probably due to relatively small sample sizes [2, 4, 9, 10], and short duration of treatment (1–2 weeks [9–11]).

The data presented here are from a large multicentre trial of patients with obstructive airways disease and a broad range of airways obstruction, airways hyperresponsiveness, and symptoms, who were followed during double-blind treatment for 2.5 yrs [5, 12]. One third of the patients was randomized to receive an inhaled corticosteroid plus a β_2-agonist.

Since no factors predictive of improvement in FEV_1 with inhaled corticosteroids are known, we related the improvement in FEV_1 to those patient characteristics that have been suggested to be prognostic factors of long-term disease outcome in asthma and COPD. Prognosis in asthma is primarily related to the level of airways obstruction and airways hyperresponsiveness [13, 14]. In COPD, prognosis is related firstly to age and initial level

of airways obstruction [15], and then to cigarette smoking, airways hyperresponsiveness, and perhaps to bronchodilator response [16–18].

Methods

Patients with respiratory symptoms were selected according to the following criteria: 1) FEV_1 4.5–1.64 residual standard deviations (RSD) below the predicted value (*i.e.* between 2.30–0.84 *l* below predicted normal FEV_1 for men, or between 1.71–0.62 *l* below predicted for women), or FEV_1/inspiratory vital capacity (IVC) more than 1.64 RSD (males 11.76%, females 10.68%) below the predicted value, provided that total lung capacity was normal (higher than 1.64 RSD (males 1.15, females 0.98 *l*) below the predicted level). For the rationale of using RSDs and for predicted values see [19, 20]. FEV_1 had to be larger than 1.2 *l*; 2) provocative concentration of histamine causing a 20% in FEV_1 (PC_{20}) ≤8 $mg \cdot ml^{-1}$; and 3) age 18–60 yrs.

Inhaled corticosteroids were tapered off, and discontinued completely 4 weeks prior to the pre-randomization visit. Other maintenance medication was withheld for at least 6 weeks (ketotifen, antihistamines), 4 weeks (cromolyn sodium), or 48 h (theophyllines) before the start of the study. Maintenance medication with oral corticosteroids was not allowed. Skin test reactivity to 12 common aeroallergens was measured intradermally [12]. A positive skin test was defined as a mean wheal size >0.7 times the histamine wheal size [12, 21].

The study was designed as a randomized, double-blind clinical trial, with three parallel treatment arms. Randomization was performed by telephoning an independent centre, using a computerized minimization method [22] with stratification by sex, age, prior use of inhaled corticosteroids, FEV_1, PC_{20}, bronchodilator response, skin test, smoking habits, and centre. This resulted in a very good balance of baseline characteristics over the treatment arms [5].

Patients were randomly allocated to one of the three double-blind regimens from identical metered dose inhalers: all patients received an inhaled β_2-agonist (BA) (terbutaline, 250 μg, 2 puffs *q.i.d.*), combined with either an inhaled corticosteroid (beclomethasone, 100 μg, 2 puffs *q.i.d.*, (BA+CS)), an inhaled anticholinergic (ipratropium bromide, 20 μg, 2 puffs *q.i.d.*, (BA+AC)), or an inhaled placebo 2 puffs *q.i.d.* (BA+PL). Additional bronchodilator medication was supplied in the form of salbutamol dry powder inhalations (400 μg), on demand. No other concomitant pulmonary medication was allowed, except during exacerbations, when a 12 day course of oral prednisolone was administered.

FEV_1 and PC_{20} were measured only during clinically stable periods, and not within 4 weeks after termination of a prednisolone course. Eight hours before these tests, all pulmonary medication was discontinued. FEV_1 was measured using water-sealed spirometers until at least three reproducible (less than 5% difference) recordings were obtained, and the highest value was then used for analyses. Reference values are those of the European Community for Coal and Steel [19]. For bronchodilator response testing, FEV_1 was measured before and 20 min after 4 separate inhalations of 250 μg of terbutaline sulphate from a metered dose inhaler, administered through a 750 ml spacer device (Nebuhaler). Histamine provocation tests were performed using a 2 min tidal breathing method [12]. For analysis purposes, patients already responding to saline or to the lowest concentration of histamine (0.03 $mg \cdot ml^{-1}$) were assigned a PC_{20} value of 0.015, being half the lowest concentration applied [12]. Total immunoglobulin E (IgE) assays were performed in a single batch, after storage of sera at -20°C. Total IgE concentrations were quantified using the enzyme immunoassay procedure (Pharmacia, Uppsala, Sweden), and expressed in $IU \cdot ml^{-1}$. Blood eosinophil numbers were counted in a Bürker chamber after staining with eosin.

Since patient characteristics at entry were very similar in all three treatment arms [12], and since the results of the intervention study for the primary end-points did not show significant treatment differences between the BA+AC and BA+PL group [5], in this report the BA+CS group is compared to the BA+PL group only. This provides an unmixed analysis of the influence of patient characteristics on the improvement in FEV_1 gained by the addition of inhaled corticosteroids to a β_2-agonist.

Statistical analysis

Inspection of individual plots of change in FEV_1 with time revealed that linear regression slopes were inappropriate in the group treated with inhaled corticosteroids, because of a stepwise increase in FEV_1 from baseline to the first follow-up visit (3 months). After the first 3 months, changes in FEV_1 could appropriately be expressed as a linear function. Therefore, the influence of baseline characteristics on change in FEV_1 was evaluated separately for the immediate improvement in FEV_1 in the first 3 months and the change in slope of FEV_1 over time from 3 months onwards. As follow-up time varied considerably because of many treatment-related withdrawals in the non-steroid groups and the early termination of the study (median follow-up 2.5 yrs [5]), the variance of the slopes of FEV_1 was not homogeneous [23]. Therefore, the unbalanced repeated measures model from the BMDP statistical package on a mainframe computer was employed [24]. This technique corrects for the fact that intra- as well as inter-individual comparisons are made, and can handle incomplete designs and "ignorable" missing data [25, 26]. In this way, all available data are used. Compound symmetry structured, unstructured (full parameterized), and random effects (on constant and slope) covariance matrix structures were compared by maximum likelihoods: the random effects models were found to be significantly better than the compound structure and not significantly different from the unstructured [27, 28]. Therefore, throughout this report random effects models are presented.

The model for the immediate (within 3 months) improvement in FEV_1 had the following general form:

$$FEV_1 = \alpha_0 + \alpha_{1..i} \times cov_{1..i} + \beta_0 \times time + \beta_{1..i} \times time \times cov_{1..i} + \gamma_0 \times treatment + \delta_0 \times time \times treatment + \delta_{1..i} \times time \times treatment \times cov_{1..i}$$

This model was compared to simple linear regression with the change in FEV_1 in 3 months as the dependent variable. The results were very similar; the unbalanced repeated measures model is presented. The model for the long-term (*i.e.* from 3 months onwards) change in FEV_1 had the following general form:

$$FEV_1 = \kappa_0 + \kappa_{1..i} \times cov_{1..i} + \lambda_0 \times treatment + \lambda_{1..i} \times treatment \times cov_{1..i} + \mu_0 \times time + \mu_{1..i} \times time \times cov_{1..i} + \nu_0 \times time \times treatment + \nu_{1..i} \times time \times treatment \times cov_{1..i}$$

where $cov_{1..i}$ signifies the i different covariates (at baseline) entered simultaneously and treatment is a dummy variable with value 0 in BA+PL and value 1 in BA+CS.

The level of obstruction was entered as Tiffeneau index (FEV_1/IVC), expressed as number of residual standard deviations below the predicted value: a larger number signifies more obstruction [19, 20]. This latter parameter of obstruction was chosen instead of the baseline FEV_1 level in order to minimize problems of regression to the mean when predicting changes in FEV_1. Calculations with PC_{20} were performed using the base-2 logarithm, as this reflects doubling doses and normalized the distribution. Blood eosinophils, total IgE and pack-years of cigarettes (1 pack of 20 cigarettes a day during one year amounts to 1 pack-year) were log_{10}-transformed, after adding one to all values in order to be able to logarithmitize zero values.

Results

The results of the intervention trial on FEV_1, PC_{20}, and exacerbation rates have been described previously [5]. Briefly, the study was terminated after a median follow-up of 2.5 yrs because of predefined, highly significant differences in withdrawal rate, FEV_1, and PC_{20} between patients treated with and without inhaled corticosteroids [5]. Forty four (48%) of patients on BA+PL were withdrawn, compared to 12 (13%) on BA+CS, ($p<0.001$). Seventy percent of withdrawals were due to increases in pulmonary symptoms [5]. The number of patients followed for 3, 9, 15 and 21 months were 89, 86, 85 and 82 in the BA+CS group and 74, 66, 55 and 49 in the BA+PL group, respectively. Baseline characteristics of the 182 patients in this report were well balanced across the two treatment arms (table 1).

Graphic presentation

The time course of prebronchodilator FEV_1 in patients with a follow-up of at least 21 months is shown in figure 1a. Figures 1b–f represent changes in FEV_1 from baseline for different subgroups. FEV_1s are sex, height, and age corrected at each time point [19].

Table 1. – Baseline characteristics by treatment group

	BA+PL	BA+CS
Patients n	91	91
Sex M/F	58/33	59/32
Age* yrs	40 (12)	40 (12)
FEV_1 prebronchodilation*		
l	2.29 (0.71)	2.38 (0.78)
% predicted	63.3 (15.7)	64.6 (15.4)
FEV_1 post terbutaline*		
% predicted	75.7 (16.5)	75.8 (16.9)
log_2 PC_{20} histamine $mg \cdot ml^{-1}$	-2.21 (2.33)	-1.62 (2.23)
Geometric mean PC_{20} $mg \cdot ml^{-1}$	0.22	0.33
Allergy:		
positive skin test n	62	70
log_{10} IgE** $IU \cdot ml^{-1}$	2.11 (0.73)	2.12 (0.73)
log_{10} eosinophils** $10^6 \cdot l^{-1}$	2.35 (0.34)	2.26 (0.47)
Smoking: never n	28	32
ex n	29	26
current n	34	33
Median pack years in lifetime smokers	11.2	11.9
Prior use of inhaled corticosteroids n	55	52

BA+PL: beta-agonist plus placebo; BA+CS: beta-agonist plus corticosteroid; *: data presented as mean and SD in parenthesis; **: SD in parenthesis; FEV_1: forced expiratory volume in one second; PC_{20}: provocative dose of histamine producing a 20% fall in FEV_1; IgE: immunoglobulin E.

Prediction of immediate (within 3 months) improvement in FEV_1 with corticosteroid therapy

In a multivariable analysis the following covariates were tested: PC_{20}, bronchodilator response, Tiffeneau index, allergy parameters (total serum IgE, number of positive skin tests, total blood eosinophils), smoking (both as number of pack-years and as dichotomous variable: current yes/no), and gender. The independent influence on FEV_1 of the covariates, and their interactions with time and treatment, are presented in table 2. The values are corrected for age and height. For the complete model, see Appendix.

With each doubling dose lower PC_{20} at baseline, there was a significantly greater improvement in FEV_1 with BA+CS compared to BA+PL (119 ml more improvement in FEV_1 in 3 months per doubling dose decrease of PC_{20}, $p<0.001$). Similarly, improvement in FEV_1 during CS therapy was significantly greater when IgE was higher (179 ml larger improvement in FEV_1 with every ten fold increase in IgE, $p=0.03$). Smokers had a 382 ml smaller improvement in FEV_1 than nonsmokers ($p=0.002$). All of these effects were independent of the simultaneous influences of the other parameters. Figures 2a and b show the continuous fashion in which FEV_1 improved with decreasing PC_{20} and increasing IgE.

The same model with specific IgE for house dust mite, or skin tests, or eosinophils, instead of IgE had much lower maximum likelihoods. Entering cumulative pack-years instead of smoking as dichotomous variable yielded a slightly lower maximum likelihood and slightly diminished the relative contribution of IgE (probably because of the age dependency of both).

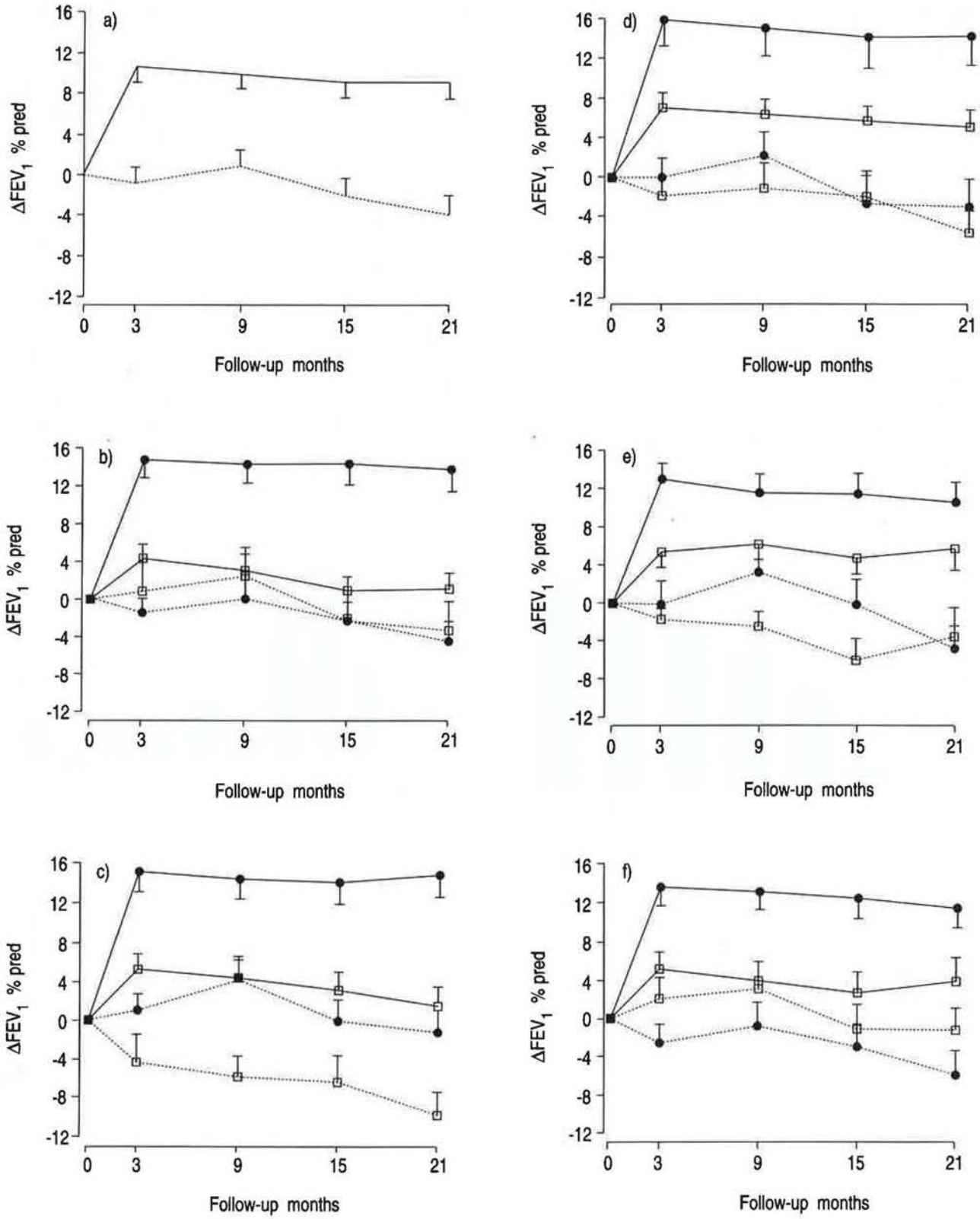

Fig. 1. – a) Change of FEV_1 % predicted from randomization for all patients with a follow-up of at least 21 months. FEV_1s are sex, height, and age corrected at every time point [18]. ——:BA+CS, β_2-agonist + corticosteroid (n=83); ·····: BA+PL, β_2-agonist + placebo (n=51). b) Stratification by level of histamine PC_{20}. ● : ≤0.5 mg·ml^{-1}; □ : >0.5 mg·ml^{-1}. c) Stratification by level of bronchodilator response. □ : ≤9% predicted; ● : >9% predicted. d) Stratification by level of obstruction expressed as Tiffeneau index (FEV_1/IVC) in number of residual standard deviations (RSDs) under predicted normal: a larger number signifies more obstruction. □: ≤3.5 RSD; ● : >3.5 RSD. e) Stratification by level of total serum IgE. □ : ≤100 IU·ml^{-1}; ● : >100 IU·ml^{-1}. f) Stratification by smoking. □: current smoker; ● : non-current smoker. FEV_1: forced expiratory volume in one second; PC_{20}: provocative dose of histamine producing a 20% fall in FEV_1; IVC: inspiratory vital capacity.

Table 2. – Independent influences of baseline characteristics on "immediate" (within 3 months) improvements in FEV_1 with inhaled corticosteroids

Covariate	Change in FEV_1 in 3 months with BA+CS compared to BA+PL ml·3 months^{-1}	p value
PC_{20} per doubling dose	-119	0.0001
BDR per 10% pred	-7	0.92
Tiffeneau per RSD	17	0.67
IgE per tenfold increase	179	0.03
Current smoking	-382	0.0015
Sex female	-204	0.10

BA+CS: beta-agonist plus corticosteroid (n=89); BA+PL: beta-agonist plus placebo (n=74); PC_{20}: provocative concentration of histamine causing a 20% fall in FEV_1 in mg·ml^{-1}; BDR: bronchodilator response on 1,000 μg terbutaline expressed as % predicted; Tiffeneau: FEV_1/IVC expressed as number of RSDs (residual standard deviations) under predicted normal; IgE: total serum IgE in IU·ml^{-1}; FEV_1: forced expiratory volume in one second; IVC: inspiratory vital capacity. For complete regression model, see Appendix.

Prediction of long-term changes in FEV_1 with corticosteroid therapy

To investigate whether the improvement in FEV_1 in the first 3 months of treatment with inhaled corticosteroids was maintained, or changed further depending on the patient baseline characteristics and the improvement gained in the first 3 months, an analysis of the long-term changes from 3 months onwards was performed.

Treatment with corticosteroids (again BA+CS as compared to BA+PL) had a significantly more positive effect on slope of FEV_1 in patients who had a higher baseline bronchodilator response: there was an 80 ml·yr^{-1} improvement in slope per 10% improvement in baseline bronchodilator response (table 3). No other covariate had an independent influence on change in FEV_1 from 3 months onwards.

Addition of an age square component did not yield better maximum likelihoods. Entering the number of pack-years smoked instead of smoking as a dichotomous variable did not change the results. Using the number

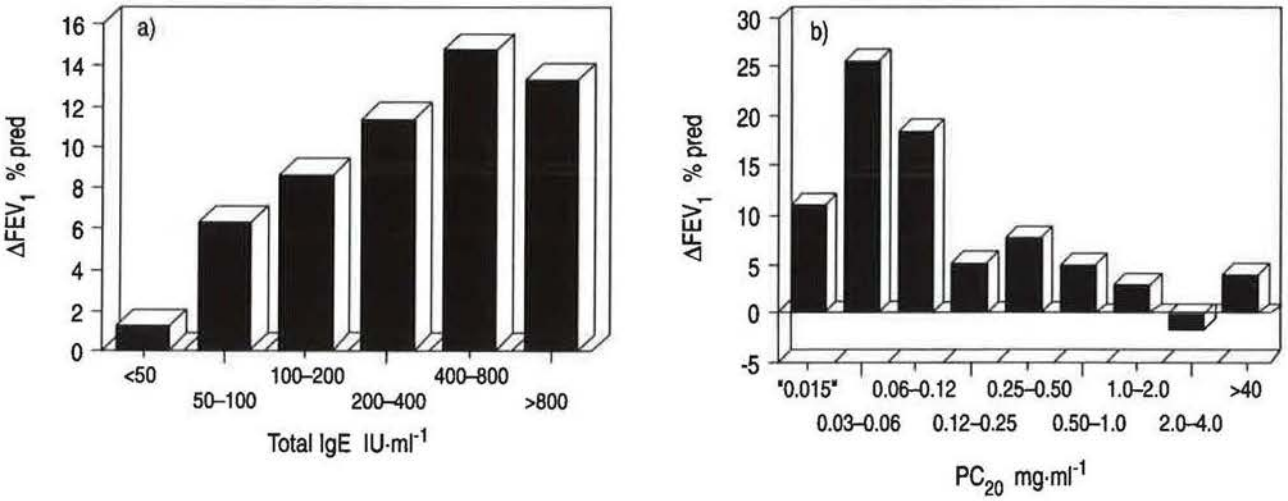

Fig. 2. – a) Increasing improvement in FEV_1 in first 3 months with increasing total serum IgE. BA+CS group only. b) Decreasing improvement in FEV_1 in first 3 months with increasing PC_{20} (histamine). BA+CS group only. The PC_{20} group "0.015" is a category with a 20% decrease in FEV_1 with the diluent (phosphate-buffered saline) or with a >20% decrease to the lowest histamine concentration (0.03 mg·ml^{-1}). For abbreviations see legend to figure 1.

Table 3. – Independent influence of baseline characteristics on changes with inhaled corticosteroids in slope of FEV_1 from 3 months onwards

Covariate	Regression coefficients: Slope of FEV_1 without use of CS ml·yr^{-1}	p value	Change in slope BA+CS compared to BA+PL	p value
PC_{20} per doubling dose	-20	0.10	17	0.27
BDR per 10% pred	-57	0.07	80	0.04
Tiffeneau per RSD	-7	0.70	22	0.30
IgE per tenfold increase	22	0.56	-28	0.56
Current smoking	-59	0.26	44	0.49
Sex female	44	0.40	-34	0.60

BA+CS: beta-agonist plus corticosteroid (n=87); BA+PL: beta-agonist plus placebo (n=65); CS: corticosteroid. For further abbreviations see legend to table 2. For complete regression model, see Appendix.

of cigarettes smoked daily at entry into the trial gave worse maximum likelihoods. Total serum IgE as parameter for allergy yielded better maximum likelihood than skin tests (number of positive skin tests, or total wheal size, or wheal size of house dust mite alone), or specific-IgE for house dust mite, or peripheral blood eosinophils.

Discussion

It is well-recognized that not all patients with obstructive airways disease respond to corticosteroids with the same improvement in FEV_1, and some patients seem not to respond at all [2, 11, 29–31]. In our analysis, airways hyperresponsiveness, nonsmoking, and total serum IgE are identified as independent predictors of improvement in FEV_1 in the first 3 months of treatment with inhaled corticosteroids in a broad group of patients with obstructive airways disease. The long-term slope of FEV_1 is favourably influenced by inhaled corticosteroid therapy in patients with a larger bronchodilator response.

Monovariable analyses of changes in FEV_1, perhaps with correction for age, height and sex, are both easy to perform and to interpret. They also provide attractive graphs, as in figures 1b–f. However, the disadvantage is an oversimplified presentation of reality, *i.e.* without simultaneous adjustment for known risk factors. Moreover, most statistical models analysing slopes of FEV_1 assume equal variances of the individual regression slopes [23], thus requiring comparable follow-up for all patients. This requirement may be fulfilled in short concise clinical or laboratory studies, but is not easily fulfilled in clinical studies with a long follow-up [32]. We therefore employed an unbalanced repeated measures method with random effects modelling [24]. Using this model, only three out of the five parameters that seemed prognostic of change in FEV_1 with CS from monovariable analyses [5], proved to be independent predictors of improvement in FEV_1 (table 3).

We are aware of only two studies in asthma providing data about subgroup analyses to predict improvement with inhaled corticosteroids from baseline patient characteristics [2, 4]. In these relatively small studies (n=32), no predictive factor could be identified. In COPD, a few studies with short courses of inhaled corticosteroids (1–2 weeks) were also unable to identify predictors of improvement in FEV_1 [9–11]. So far, in COPD, more effort has been put into identifying predictors of improvement on oral corticosteroids. However, no consistent pattern has emerged from these studies: bronchodilator response, sputum and blood eosinophilia, have been found to be weak predictors of improvement by some authors but not by others [9, 33–37]. Our study differs from earlier reports, in that a large group of 182 patients with obstructive airways disease was investigated, who had a broad range of baseline characteristics (table 1), thus enabling a successful analysis of the relationship between patient characteristics and improvement in FEV_1 with inhaled corticosteroids. The choice of covariates in our models, (*i.e.* the possible indicators of a favourable response to inhaled corticosteroids), was based on factors reported to be prognostic of long-term disease outcome on the one hand, and on the few predictors of favourable treatment response suggested from earlier studies with oral corticosteroids on the other.

Airways hyperresponsiveness, total IgE, and smoking habits, were found to be independent predictors of an immediate (within 3 months) treatment effect of inhaled corticosteroids (table 2). One of the most intriguing results of this study is the two-faced predictive value of baseline airways hyperresponsiveness on short-term changes in FEV_1. In the group that used only a β_2-agonist, more severe hyperresponsiveness was associated with steeper decline in FEV_1 in the first 3 months of treatment. This finding is compatible with the steeper decline in FEV_1 in patients with more severe hyperresponsiveness found in non-controlled follow-up studies [13, 14, 16–18], and perhaps with the suggested detrimental influence of bronchodilators [38]. By contrast, in patients given inhaled corticosteroids, more severe baseline hyperresponsiveness was associated with a larger increase in FEV_1 during the first 3 months of treatment. This importance of airways hyperresponsiveness is well in line with the fact that the degree of airways obstruction is partly determined by inflammatory changes (by increases in airway wall thickness because of cellular infiltrations, hyperaemia, oedema; and by decreases in luminal diameter by increased bronchomotor tone and intraluminal secretions), and airways hyperresponsiveness is thought to reflect the degree of airways inflammation in asthma and COPD [39–41]. Whether higher doses of inhaled corticosteroids for a longer duration of time would further normalize the lung function is a matter of speculation, but it has been suggested that even after 10 yrs of treatment with inhaled corticosteroids (200–800 μg daily) inflammation persists [42].

Total IgE proved to be a better predictor of inhaled corticosteroid response than other allergy parameters (skin tests, specific-IgE for house dust mite, and blood eosinophils), when corrected for age and sex, and independent of the effect of smoking. This suggests that total allergenic load, expressed as total IgE, is more important in modulating airways hyperresponsiveness than allergy to a specific single allergen, as expressed by skin tests or specific IgE [43, 44]. It has been shown in epidemiological studies, however, that skin test reactivity and blood eosinophilia are associated with distinct patterns of respiratory symptoms as well [45, 46].

The improvement in FEV_1 with inhaled corticosteroids in the first three months of treatment was maintained thereafter irrespective of most baseline characteristics: only bronchodilator response was an independent predictor of change in long-term slope with CS therapy. We are not aware of other data concerning the influence of the bronchodilator response on the long-term course of FEV_1 in patients treated with inhaled corticosteroids. Contradictory results have been reported on the predictive value of the bronchodilator response for prognosis without maintenance corticosteroids: a larger bronchodilator response has been associated both with an accelerated [16, 47, 48], and with a diminished rate of decline in FEV_1 [17, 49]. In our study, without CS treatment, a larger bronchodilator response was associated with a steeper decline (57 $ml \cdot yr^{-1}$

more decline per 10% predicted increase in bronchodilator response, p=0.07) (table 3), but with CS treatment, a larger bronchodilator response was associated with a more favourable rate of decline (80 ml·yr^{-1} better, p=0.04) (table 3). High reversibility, a larger bronchodilator response, as such may indicate the need for anti-inflammatory therapy and thus be a prognostic sign that physicians are able to measure and respond to with the administration of inhaled corticosteroids.

We could not confirm a relationship between airways hyperresponsiveness and long-term rate of decline in FEV_1 [13, 14, 16–18]. It is possible that the regular and well-monitored treatment of patients in our study obscured such a relationship, or that the follow-up was too short for such an effect to become apparent. This may also be responsible for the lack of independent effect of level of obstruction and smoking on the course of FEV_1, which is in contrast to earlier studies [16, 50, 51]. Employing a different parameter of smoking (number of pack-years, or number of cigarettes smoked daily at entry into the trial) did not yield different results. The difference could also be attributable to a more marked "healthy smoker" effect in this clinical population.

It is important to indicate the clinical implications of our results: these analyses show a larger "immediate" (within 3 months) effect of inhaled corticosteroids on FEV_1 per tenfold increase in IgE, per doubling dose decrease in PC_{20}, and when not smoking (figs. 2a and b). The effects are, however, not limited to the few patients with the highest IgE, lowest PC_{20}, who do not smoke. We have demonstrated separately that there was a positive, though not invariably a large, effect of inhaled corticosteroids in all subgroups of patients (old and young, high and low PC_{20}, high and low bronchodilator response, (non-)allergic, (non-)smoking *etc.* [5]).

In conclusion, airways hyperresponsiveness, IgE, and nonsmoking are independent predictors of improvement in FEV_1 in the first 3 months of treatment with inhaled corticosteroids in patients with obstructive airways disease. A larger bronchodilator response is associated with a more favourable long-term course of FEV_1 in patients receiving inhaled corticosteroids.

Appendix with complete regression models

Table A1

α_0=303, β_0=-99, γ_0=-19, δ_0=-19

	α_i	β_i	δ_i
Height	22***		
Age	21***		
Sex	-410***	-30	-204
PC_{20}	48**	50*	-119***
BDR	27	143**	-7
Tiffeneau	-261***	-8	17
IgE	60	-18	179*
Smoking	-16	159	-382**

Model for Table 2: $FEV_1 = \alpha_0 + \alpha_{1..i} \times cov_{1..i} + \beta_0 \times time + \beta_{1..i} \times time \times cov_{1..i} + \gamma_0 \times treatment + \delta_0 \times time \times treatment + \delta_{1..i} \times time \times treatment \times cov_{1..i}$

α, γ in ml; β, δ in ml·3 months^{-1}

*: p≤0.05; **: p≤0.01; ***: p≤0.001, abbreviations and other units as in table 2.

Table A2

κ_0=115, λ_0=-510, μ_0=-28, ν_0=-61

	κ_i	λ_i	μ_i	ν_i
Height	25***			
Age	-22***			
Sex	-413**	-380*	44	-34
PC_{20}	123***	-155***	-20	17
BDR	181**	65	-57	80*
Tiffeneau	-251***	-25	-7	22
IgE	-99	385***	22	-28
Smoking	30	-179	-59	44

Model for Table 3: $FEV_1 = \kappa_0 + \kappa_{1..i} \times cov_{1..i} + \lambda_0 \times treatment + \lambda_{1..i} \times treatment \times cov_{1..i} + \mu_0 \times time + \mu_{1..i} \times time \times cov_{1..i} + \nu_0 \times time \times treatment + \nu_{1..i} \times time \times treatment \times cov_{1..i}$

κ, λ in ml; μ, ν in ml·yr^{-1}

*: p≤0.05; **: p≤0.01; ***: p≤0.001; abbreviations and other units as in table.

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