

Accuracy of eosinophils and eosinophil cationic protein to predict steroid improvement in asthma

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Summary

Background There is a large variability in clinical response to corticosteroid treatment in patients with asthma. Several markers of inflammation like eosinophils and eosinophil cationic protein (ECP), as well as exhaled nitric oxide (NO), are good candidates to predict clinical response.

Aim We wanted to determine whether we could actually predict a favourable response to inhaled corticosteroids in individual patients.

Methods One hundred and twenty patients with unstable asthma were treated with either prednisolone 30 mg/day, fluticasone propionate 1000 µg/day b.i.d. or fluticasone propionate 250 µg/day b.i.d., both via Diskhaler. They were treated during 2 weeks, in a double-blind, parallel group, double dummy design. We measured eosinophils and ECP in blood and sputum, and exhaled nitric oxide as inflammatory parameters before and after 2 weeks in order to predict the changes in forced expiratory volume in 1 s (FEV₁), provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀ Mch), and asthma quality of life (QOL). Secondly, to test whether these results were applicable in clinical practice we determined the individual prediction of corticosteroid response.

Results We found that changes in FEV₁, PC₂₀ Mch and QOL with corticosteroids were predominantly predicted by their respective baseline value and to a smaller extent by eosinophils in blood or sputum. ECP, measured in blood or sputum, was certainly not better than eosinophils in predicting clinical response to corticosteroids. Smoking status was an additional predictor for change in FEV₁, but not for change in PC₂₀ Mch or QOL. Prediction of a good clinical response was poor. For instance, high sputum eosinophils ($\geq 3\%$) correctly predicted an improvement in PC₂₀ Mch in only 65% of the patients.

Conclusion Our findings show that baseline values of the clinical parameters used as outcome parameters are the major predictors of clinical response to corticosteroids. Eosinophil percentage in blood or sputum adds to this, whereas ECP provides no additional information. Correct prediction of clinical response in an individual patient, however, remains poor with our currently used clinical and inflammatory parameters.

Keywords asthma, clinical response, corticosteroids, ECP, eosinophils, inflammation, nitric oxide, quality of life

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Introduction

Inhaled corticosteroids are currently the most frequently used medication for maintenance asthma treatment. All international guidelines advocate an early introduction of corticosteroids to control asthma symptoms and to improve lung function by reducing airway inflammation [1–4]. It has now been well established that clinical parameters like lung function, airway hyper-responsiveness and quality of life improve with corticosteroid treatment [5–7]. It is generally assumed that reduction of inflammation causes the improvement in the clinical

state of asthma [8–15]. It would be relevant to predict the response to corticosteroid treatment as not all individuals respond similarly to corticosteroids [16, 17]. Knowing which individual has a less favourable response could identify those patients who would benefit from higher doses of inhaled steroids or from additional other therapy.

We had two main questions:

- Can we predict the clinical response, as measured by change in FEV₁, PC₂₀ Mch and asthma quality of life (QOL) in unstable asthmatics during a 2-week treatment with corticosteroids [18] using clinical and inflammatory parameters such as blood and sputum eosinophils and eosinophil cationic protein (ECP), and exhaled nitric oxide in a linear regression model?
- How good is this prediction of steroid response in individual patients? Or, in other words, do the results of the analyses have practical implications in day-to-day treatment?

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Patients and methods

Patients

Patients with symptoms and with a diagnosis of asthma, aged 18 to 56 years old, were included if they met the following criteria: a concentration of methacholine (Mch) causing a 20% fall in FEV_1 (PC_{20}) ≤ 8 mg/mL, at least one positive skin test out of 17 common aeroallergens tested, reversibility to β_2 -agonist $\geq 9\%$ of the predicted FEV_1 , and ability to expectorate sputum after hypertonic saline inhalation.

Study design

Inhaled corticosteroids were tapered and when possible discontinued completely at least 3 weeks prior to the randomization visit. When patients experienced a worsening of their asthma before complete discontinuation of inhaled corticosteroids for 3 weeks, they were asked to visit the hospital for earlier randomization and inclusion. Randomization was performed by a computerized minimization method [19] with stratification according to age, previous dose of inhaled corticosteroids, $FEV_1\%$ predicted, reversibility after 200 μ g of salbutamol, PC_{20} Mch, smoking status and serum IgE. The study had a 2-week, double-blind, three-arm parallel group, double dummy design. Medication was supplied by GlaxoWellcome, Stevenage, UK. Patients received either prednisolone 30 mg/day or fluticasone propionate 1000 μ g via Diskhaler dry powder inhalation b.i.d. (FP2000), or fluticasone 250 μ g b.i.d. (FP500) also via Diskhaler. Rescue medication consisted of salbutamol 400 μ g via Diskhaler. No other concomitant pulmonary medication was allowed. Measurements at the start and after 2 weeks of treatment were performed on two consecutive days. On the first day blood sampling, exhaled nitric oxide (NO), quality of life questionnaire (QOL), lung function, reversibility after salbutamol and sputum induction were performed. On the second day airway hyper-responsiveness was measured by Mch challenge. The study protocol was approved by the local medical ethics committee and all participants gave their written informed consent.

Lung function

FEV_1 was measured with a calibrated water-sealed spirometer according to standardized guidelines. At least three reproducible values were obtained [20]. The highest value was used for analysis. Mch provocation test was performed with a 2-min tidal breathing method. FEV_1 was measured before and 20 min after 200 μ g of salbutamol to test reversibility.

Exhaled nitric oxide

Exhaled NO was measured using a chemiluminescence analyser (CLD 700 AL, ECO physics, Switzerland) with a lowest detection limit of 1 part per billion (p.p.b.) and a resolution of ± 1 p.p.b. The sampling flow was 600 mL/min and the response time < 7 s, including lag and rise time [21]. Exhaled NO was measured by tidal breathing method as described by Alving [22]. Subjects, wearing a nose clip, inhaled air from a Douglas bag with low NO concentration (< 3 p.p.b.) and breathed quietly during 5 min through a two-way Hans-Rudolph® valve. Exhaled air was collected in a second Douglas bag from which samples were drawn. Tidal volume and minute ventilation were measured with a pneumotachograph (Jaeger, Hoechberg, Germany).

Quality of life

An interviewer-administered asthma questionnaire was used as described by Juniper [18]. This questionnaire contains 32 items divided into four groups (symptoms, anxiety, environmental factors and activities).

Induced sputum

Fifteen minutes after salbutamol (200 μ g) inhalation, hypertonic saline (3%, 4% and 5%) generated by an ultrasonic nebulizer (Ultraneb 2000, DeVillbiss, Somerset, Pennsylvania, USA) was nebulized for each concentration during 7 min [23, 24]. Output of the nebuliser was calibrated at 1.5 mL/min. Subjects inhaled the hypertonic saline and were encouraged to cough and expectorate sputum into a container. The weight of the induced sputum was measured. An equal volume of dithiothreitol 0.1% (Sputalysin 10%, Boehringer Diagnostics Inc., Sommerville, NY, USA) was added to the weight of the sputum. The sample was vortexed and placed in a shaking water bath of 37 °C for 15 min and filtered through a nylon (48 μ m) gauze. A haematocytometer was used to count total cell number, viability and squamous epithelial contamination of the cell suspension. The sputum sample was centrifuged (10 min, 450 g, 4 °C). The cell pellet was resuspended in PBS buffer and cytopins were stained by May-Grünwald-Giemsa. At least 200 non-squamous cells were counted separately by three investigators blinded to the treatment code, and averaged cell differentials are presented.

Biochemical assays

The concentration of ECP in serum (se) and sputum (sp.) supernatant were measured using a fluoroenzyme assay (ImmunoCAP ECP, Pharmacia, Uppsala, Sweden). Blood samples were kept 1 h at room temperature (21 °C), after which serum was obtained by centrifugation at 960 g for 10 min and stored at -20 °C for later analyses. Cell counts were performed in the routine university laboratory by flow cytometry technique.

Statistical methods

All calculations of PC_{20} were performed with the base-2 logarithm ($\log_2$), reflecting doubling concentrations and normalizing the distribution. Patients already responding to saline were assigned a PC_{20} value half of the lowest concentration applied. Patients not responding to the highest concentration of Mch were assigned a value twice the highest concentration applied. Univariate analysis was performed for all four eosinophilic variables (eosinophils and ECP in blood and sputum), exhaled NO and smoking status. To determine independent prognostic factors of change in FEV_1 , PC_{20} Mch or QOL, a multiple regression analysis was employed. Age, gender and treatment were entered as covariates into all models. The following variables were tested in a stepwise procedure: $FEV_1\%$ pred., smoking status, serum IgE, exhaled NO, PC_{20} Mch, blood eosinophils and sputum eosinophils. The resulting models for FEV_1 , PC_{20} Mch and QOL all contained one eosinophil parameter. The relative value of the eosinophil parameters was tested by re-running the final model four times, each time with only one of the following parameters entered separately: sputum eosinophils and ECP, and blood eosinophils and ECP. The contribution of the different variables to the model was calculated by the squared partial correlation coefficient.

For clinical practice cut-off points can be useful for decisions on treatment of an individual patient. For example, sputum eosinophils > 3% has been suggested to signify steroid responsiveness [25]. The following cut-off points, determined from published reports, were applied: change in FEV₁%pred. at 9% pred. [26], PC₂₀ Mch at one doubling concentration [27], and QOL at 0.5 point [18]. Cut-off point for sputum eosinophils was set at 3% [25, 28], blood eosinophils at 3% [29], sputum ECP at 120 µg/L [28], and serum ECP at 15 µg/L [30]. A value of $P < 0.05$ was considered to be significant. Where applicable, the two tailed P -values were chosen.

Results

One hundred and twenty patients were enrolled into the study. Two of the 120 patients were not able to visit the hospital 2 weeks after start of the treatment (one pregnancy and one loss of study medication) and have been left out of the analyses. The baseline characteristics of the patients are presented in Table 1. There were no significant differences between the three treatment groups at the start of the study. The comparison of the three treatment regimes has been described separately, showing that the improvement in PC₂₀ Mch with FP2000 was

Table 1. Baseline characteristics

	Prednisolone	FP2000	FP500
No. of patients	40	40	40
Age (yr)	27 (18–53)	28 (18–48)	27 (18–56)
Gender M/F	14/26	14/26	14/26
Smoking (%)			
Current	28	33	28
Non-smoker	72	67	72
ICS use at baseline (no/yes)	13/27	13/27	10/30
FEV ₁ %pred.	80 (65;91)	79 (67;91)	81 (70;96)
PC ₂₀ Mch (mg/ml)	0.51 (0.18;1.80)	0.59 (0.18;2.00)	0.42 (0.18;1.48)
QOL*	5.5 (4.9;5.9)	5.6 (4.9;6.2)	5.5 (4.9;6.0)
Reversibility%pred.	12.0 (9.2;17.8)	11.4 (9.0;17.2)	12.3 (9.2;14.4)
IgE (IU/mL)	251 (157;615)	252 (86;554)	184 (98;631)
NO (p.p.b.)	15.2 (11.8;20.7)	16.0 (10.6;20.9)	13.0 (9.0;17.8)
Eos bl (%)	5.8 (3.6;8.0)	5.0 (4.0;6.8)	5.1 (2.8;7.9)
Eos sp (%)	5.5 (2.0;14.7)	5.0 (1.0;8.0)	5.0 (1.67;12.0)
ECP se (µg/L)	19.5 (10.4;26.8)	13.3 (9.9;22.0)	17.1 (9.3;24.9)
ECP sp (µg/L)	78.4 (28;292)	73.6 (33;250)	95.8 (46;233)

Data are expressed as medians with interquartile ranges, unless stated otherwise. FP2000 = 2000 µg/day of fluticasone; FP500 = 500 µg/day of fluticasone. Age is expressed as medians with ranges; eos = eosinophils, expressed as % in leucocyte differential count; ECP = eosinophilic cationic protein; se = serum; bl = blood; sp = sputum; ICS = inhaled corticosteroids; *QOL maximum score is 7.

Table 2. Monovariate correlations of inflammatory parameters at baseline with improvement in clinical parameters during therapy

	Eos blood	Eos sputum	ECP serum	ECP sputum	NO	Non-smoker
Δ FEV ₁ %pred.	0.40**	0.42**	0.26*	0.27*	0.25*	NS
Δ PC ₂₀ Mch	0.20*	0.25**	0.20*	NS	NS	0.19*†
Δ QOL	0.41**	0.32**	0.33**	0.19*	0.26**	NS

For abbreviations see Table 1. * $P < 0.05$, ** $P < 0.01$. †Non-smoking versus current smoking, Spearman correlation coefficient.

significantly larger than with prednisolone ($P = 0.02$). FEV₁ increased within all three treatment groups, with a trend in favour of FP2000. Eosinophils and ECP in induced sputum decreased significantly in all three groups. Furthermore, we found that blood eosinophils ($P \leq 0.001$) and ECP ($P = 0.02$) decreased significantly more with prednisolone than with FP500, and more with FP2000 than with FP500 ($P = 0.003$) [23].

Monovariate correlation of inflammatory parameters with change in FEV₁, PC₂₀ Mch or QOL

The numbers of eosinophils in blood and sputum at baseline correlated more closely and positively with changes in clinical parameters than levels of ECP or exhaled NO at baseline (Table 2). Non-smokers had a larger improvement in PC₂₀ Mch than smokers, but not a larger improvement in QOL or FEV₁.

Independent prediction of improvement in FEV₁ during corticosteroid therapy

FEV₁, PC₂₀ Mch, eosinophil parameters and exhaled NO all correlate with each other to a certain degree. Therefore, independent predictors of improvement were explored in a multiple linear regression model. Age, gender and medication group were forced into each model. It was found that a change in FEV₁ was predominantly predicted by baseline FEV₁ (Fig. 1). Furthermore, eosinophils and ECP in blood and sputum all independently provided additional prediction of improvement in FEV₁ (Fig. 1). Blood and sputum eosinophils were better predictors than ECP. Smoking status was also a significant predictor in addition to sputum ECP, but not in addition to blood or sputum eosinophilic parameters. In Table 3 we present the relative contribution of the number of eosinophils and other inflammatory parameters to the explanation of the remaining variance. Figure 2 depicts the sputum eosinophilia dependency of the steroid-induced response in FEV₁.

Independent prediction of improvement in PC₂₀ methacholine during corticosteroid therapy

In the model containing age, gender and medication group, baseline PC₂₀ Mch predominantly explained the change in PC₂₀ Mch (18%). Only sputum eosinophils added significant information regarding the remaining variance (5%, Fig. 3). Blood eosinophils and ECP in blood and sputum were not significant predictors in a model also containing baseline PC₂₀ Mch.

Independent prediction of improvement in asthma quality of life during corticosteroid therapy

Change in QOL was predominantly explained by baseline QOL, in a model containing gender, age and medication group.

Fig. 1. Prediction of corticosteroid-induced improvement in FEV₁ by baseline parameters, expressed as partial cumulative squared correlation coefficients derived from multiple linear regression models. Eosinophils and ECP in blood and sputum were entered separately into the model. Stacked bars represent percentage of the remaining variance explained by factor.

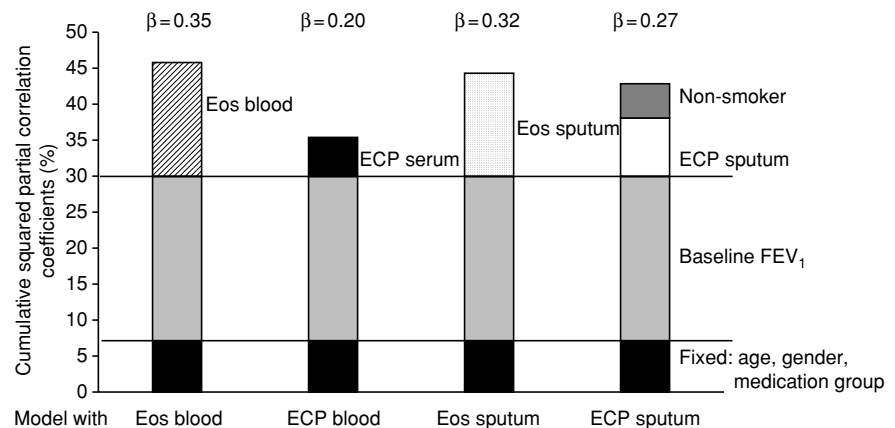


Table 3. Multiple linear regression models with eosinophils or ECP in sputum or blood entered separately

	Total explained variance R ² (standardized regression coefficient, β)			
	Eos blood	Eos sputum	ECP blood	ECP sputum
Δ FEV ₁	43% (0.35)	41% (0.32)	36% (0.20)	41% (0.27)
Δ Mch	*	21% (0.20)	*	*
Δ QOL	49% (0.29)	43% (0.22)	48% (0.22)	*

For abbreviations see Table 1. All models also contained baseline, age, gender and medication group. *Not included in model ($P > 0.05$).

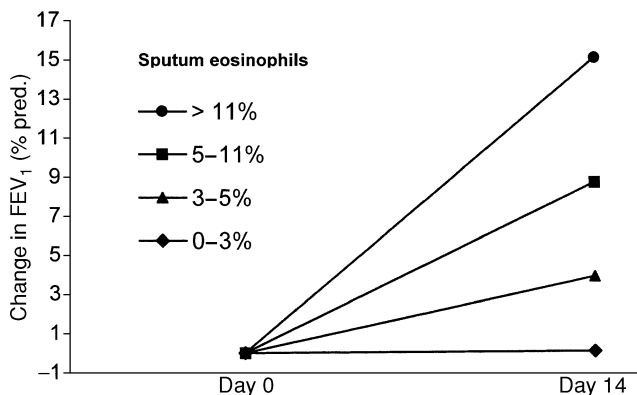


Fig. 2. Change in FEV₁% predicted subdivided by baseline sputum eosinophils (%) (the division was so as to have four equally large groups).

Eosinophils in blood and sputum significantly explained an additional 15 and 8% of the remaining variance of the models, respectively. In the model that included blood eosinophils, total serum IgE significantly added 5% to the remaining variance, while in the model with serum ECP again serum IgE and also FEV₁ added significantly to the remaining variance (Fig. 4).

Prediction of improvement in individual patients

To determine whether commonly applied cut-off points for the eosinophil parameters accurately predicted the change in FEV₁, PC₂₀ Mch and QOL with any accuracy in individual patients, two by two tables were constructed (Table 4). Although all cut-off points gave significant separation of responders and

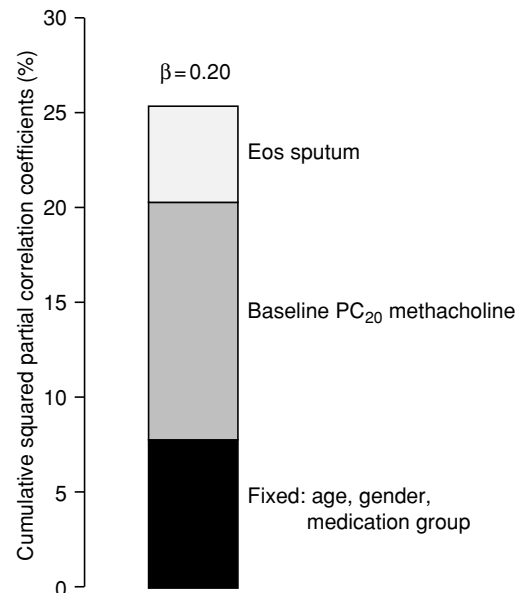


Fig. 3. Prediction of corticosteroid-induced improvement in PC₂₀ Mch by baseline parameters, expressed as partial cumulative squared correlation coefficients derived from multiple linear regression models. Eosinophils and ECP in blood and sputum were entered separately into the model. Stacked bars represent percentage of the remaining variance explained by factor.

non-responders, the percentage correct classifications remained low (range 44 to 66%). Individual sputum eosinophil numbers and steroids-induced changes in FEV₁ are shown in Fig. 5 demonstrating that a sputum eosinophil percentage above 3% at baseline still poorly predicted the individual response.

Discussion

The present study shows that prediction of a clinical response to corticosteroids as defined by FEV₁, PC₂₀ methacholine or quality of life, is mainly determined by its own baseline value. The most important additional predictors are numbers of blood and sputum eosinophils. Notwithstanding the significance of eosinophil parameters, in the individual patient the prediction of a significant improvement in FEV₁, PC₂₀ Mch and QOL remains poor. Furthermore, we found that eosinophils in

Table 4. Cut-off points of clinical and inflammatory parameters at baseline versus changes in FEV₁, PC₂₀ Mch, or QOL

	Eos blood (%)			Correct classification (%)	Eos sputum (%)			Correct classification (%)	ECP serum (µg/L)			Correct classification (%)	ECP sputum (µg/L)			Correct classification (%)
	< 3	≥ 3			< 3	≥ 3			< 15	≥ 15			< 120	≥ 120		
Δ FEV ₁ %pred.	< 9	17	59	44	34	46	57		42	38	58		53	26	66	
	≥ 9	2	31		4	31			10	25			13	22		
Δ PC ₂₀ Mch (DC)	< 1	8	28	63	19	21	65		21	18	56		21	17	47	
	≥ 1	10	58		18	53			30	41			41	30		
Δ QOL	< 0.5	13	39	60	25	31	63		32	24	63		37	19	58	
	≥ 0.5	5	52		12	47			19	40			29	29		

DC=doubling concentration. For abbreviations see Table 1. Total number of patients differs slightly for the presented variables because not all parameters were complete during both visits.

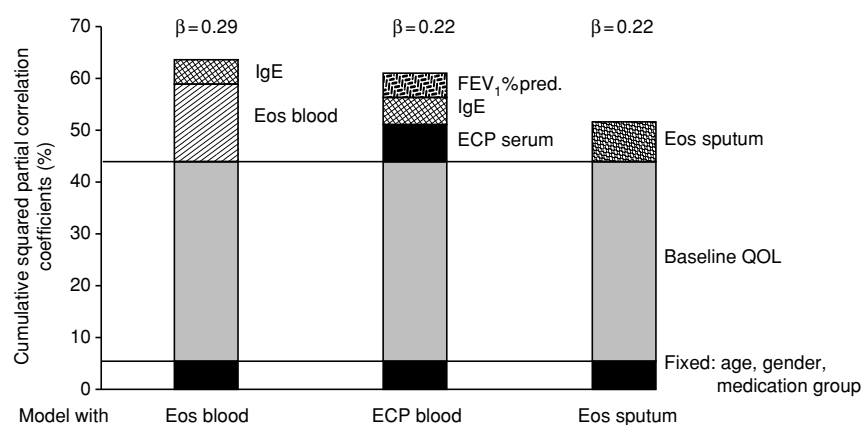


Fig. 4. Prediction of corticosteroid-induced improvement in quality of life by baseline parameters, expressed as partial cumulative squared correlation coefficients derived from multiple linear regression models. Eosinophils and ECP in blood and sputum were entered separately into the model. Stacked bars represent percentage of the remaining variance explained by factor.

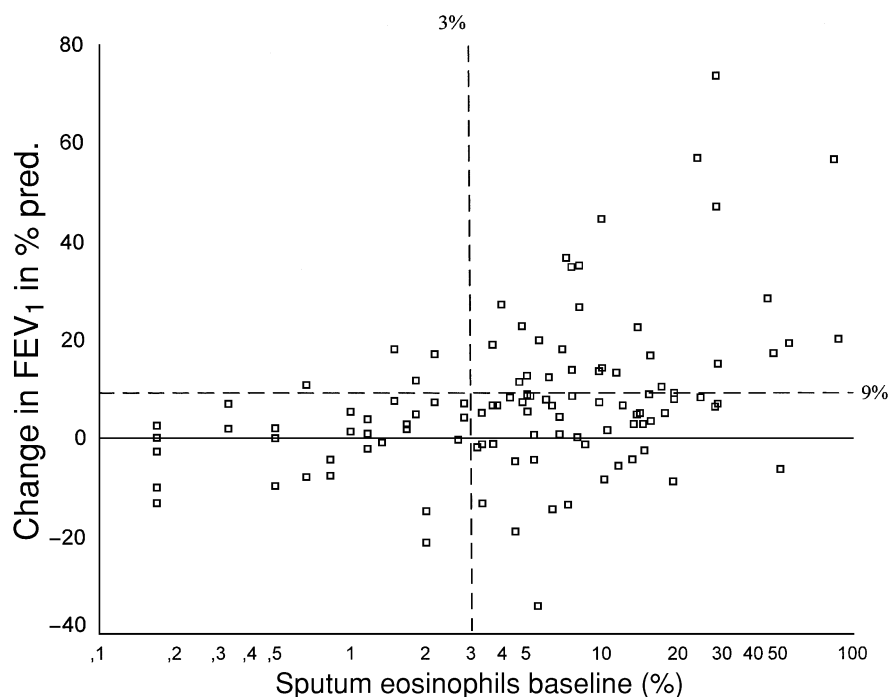


Fig. 5. Scatterplot of eosinophils at baseline and change in FEV₁%pred. with corticosteroids. Dashed lines represent commonly used cut-off points.

blood or sputum better predicted changes in clinical variables than the respective ECP values.

Finding an individualized optimal corticosteroid dose per patient has traditionally been a trial and error process. This is even more important as some patients with asthma do not seem to respond to corticosteroids at all. A good prediction of clinical response would be useful to patients and doctors.

Two earlier studies investigating whether one can predict a clinical response to corticosteroids were unable to find such predictors [31, 32]. In these studies the numbers of patients were much smaller ($n = 30$ and $n = 32$), while measurements of eosinophils, ECP in sputum and exhaled NO were not available. However, a recent study from Little et al. showed that eosinophils ($> 3\%$) and exhaled NO (> 9 ppb) predicted improvement in FEV₁ after oral prednisolone during 2 weeks of therapy with a sensitivity of 76% and a specificity of 75% [15]. Therefore, as in our study, on a group level eosinophils are a good predictor of corticosteroid response. Kerstjens et al., in a larger group of patients ($n = 182$) [33], found that a higher total serum IgE, lower PC₂₀ histamine and non-smoking predicted a larger improvement in FEV₁ with 800 µg of beclomethasone after 3 months of treatment. However, blood eosinophils did not contribute to a better prediction.

Several explanations are possible for differences between their and our results. First, treatment medication consisted of 800 µg/day of beclomethasone compared with 500 or 2000 µg/day of fluticasone or oral prednisolone (30 mg/day) in our study. The latter two treatments (FP2000 and oral prednisolone) have been suggested to decrease blood eosinophils to a larger extent than to FP500 [34, 35]. Secondly, the previous study included both asthma patients but also COPD patients. Therefore, as can be expected, the absolute eosinophil numbers in blood were lower compared with our data (182×10^6 vs. 390×10^6 eosinophils/L in our study). Moreover, it is known that the numbers and activation state of blood eosinophils are generally higher in asthma than in COPD [36]. Thirdly, they investigated stable patients, whereas our group of patients had predominantly unstable asthma when treatment was instituted. Furthermore, we and others [31–33, 37] have demonstrated a relatively weak correlation between eosinophil changes with corticosteroid treatment and changes in FEV₁ and PC₂₀ Mch. We suggest that this is also due to a difference in time frame: changes in eosinophils occur much more rapidly than changes in FEV₁, which in turn occur more rapidly than improvement in PC₂₀ Mch [38].

Long-term follow-up has shown that FEV₁ improvement stabilizes before 3 months, while PC₂₀ Mch takes up to 6 months with smaller improvements up to at least 1 year [6]. In our study patients were treated just for a 2-week period (a longer treatment period for the oral prednisolone group was not feasible), suggesting that FEV₁ might not have reached its maximal improvement. This assumption is also supported by Faul and coworkers [39], who found an improvement in FEV₁ up to 8 weeks after treatment with fluticasone 2000 µg/day in asthmatics. Finally, and probably the most important reason, is that we included baseline values of the predicted variables in our multiple linear regression model, which had a very strong contribution.

Correction for baseline leads to a component regression to the mean, i.e. low baseline values of a patient can improve considerably while a near normal value can only improve

marginally. However, it is important for clinical practice to know that baseline values predict which patients will respond positively to corticosteroids. When we performed the multiple regression analyses without baseline values in the models, predictions of eosinophils and ECP remained unchanged. However, in this case a lower PC₂₀ Mch and non-smoking also predicted a better improvement in FEV₁, which is in line with observations of Kerstjens et al. [33].

We found that eosinophil parameters were the second most important predictors of corticosteroid response. We realize that our results pertain only to a 2-week treatment period. However, the observed decrease of eosinophils in response to corticosteroids after 2 weeks of treatment seems a sufficient period to observe maximum decrease of eosinophils. This is supported by studies from Pizzichini, who showed a rapid decrease in numbers of eosinophils in sputum within 2 days. While two previously published studies support our findings [40, 41], others did not find eosinophils to be a good predictor [31–33].

Which role does ECP play in this response to corticosteroids? Several studies have shown that blood eosinophils and ECP as inflammatory markers cross-sectionally correlate relatively well with FEV₁ but not with PC₂₀ Mch [11, 42]. Our study, in a large group of asthmatics, is the first to investigate whether ECP or eosinophils are superior in predicting the changes in FEV₁, PC₂₀ Mch or QOL. During a 2-week treatment period, numbers of eosinophils in sputum and blood before starting corticosteroid therapy correlated more closely with changes in clinical parameters (FEV₁ and hyper-responsiveness) than levels of sputum and blood ECP.

To our knowledge, our study is the first to assess which clinical and inflammatory parameters may predict a change in asthma QOL. We found blood eosinophils and not sputum eosinophils to be the most important additional predictor, next to baseline QOL. This is in contrast to PC₂₀ Mch, in which case sputum eosinophils better predicted the change than blood eosinophils.

Eosinophils were generally better predictors than ECP. Sputum eosinophils were slightly better than blood eosinophils for predicting changes in FEV₁ and PC₂₀ Mch, whereas the reverse was true for predicting quality of life changes. Our results need to be confirmed, but the relatively small differences between blood and sputum eosinophils in all analyses would favour the use of blood eosinophils in clinical practice, because of ease of measurement. From our data there is no role for the use of ECP in clinical management of asthma treatment.

Both higher number of sputum eosinophils and higher levels of exhaled NO are thought to reflect a larger inflammatory burden in the airway wall of asthmatics [22]. We therefore anticipated that exhaled NO would predict a response to corticosteroids as well. In contrast to the results with eosinophils, we found that exhaled NO did not give a significant independent prediction of changes in FEV₁, PC₂₀ Mch and QOL (although in the monovariate analysis it did correlate to improvement in FEV₁ to some degree). The question arises whether the level of exhaled NO reflects long-term airway inflammation. It has been shown that production of exhaled NO is regulated by different types of NO synthases. Especially the inducible form of NO synthase gives rise to very rapid changes (within minutes) in NO levels, which may thus result in a poor correlation between exhaled NO and above-mentioned changes in clinical variables measured over a 2-week period [43, 44].

In conclusion, changes in FEV₁, PC₂₀ Mch or QOL with corticosteroids are mainly predicted by their own baseline values. The second most important predictive parameter is the number of sputum and blood eosinophils, yet with relatively small additional predictive value. The individual prediction of a significant improvement in a given clinical parameter is still poor. ECP in sputum or blood does not provide more information in predicting the change in FEV₁, PC₂₀ Mch or QOL than eosinophil counts do, and from our study we see no use for their measurement.

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