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Sputum inflammation predicts exacerbations after cessation of inhaled corticosteroids in COPD☆

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KEYWORDS
Inhaled corticosteroids;
Airway inflammation;
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Summary
Introduction: The GOLD guidelines advocate not to institute inhaled corticosteroids (ICS) in patients with mild-to-moderate COPD. However, many patients do use ICS and in some patients, withdrawal is associated with deteriorating lung function and increased exacerbation rates. Unfortunately, physicians do not know in which patients they can stop ICS treatment safely.
Aim: To identify predictors of COPD exacerbations after ICS withdrawal.
Methods: During ICS treatment, post-bronchodilator spirometry, body plethysmography, and health status assessment were performed in 68 COPD patients using ICS. Additionally, sputum cell differentials, supernatant leukotriene B_4, eosinophilic cationic protein, and myeloperoxidase, serum C-reactive protein and soluble intracellular adhesion molecule, and urinary desmosine were assessed. Sputum was also analysed for mRNA levels of haemoxygenase-1, tumour necrosis factor-α, RANTES, interleukin 5(IL-5), IL-10, IL-12, IL-13, transforming growth factor-β, and interferon-γ.
Statistics: Cox regression analyses were performed using time to exacerbation as outcome variable to identify significant hazards for a COPD exacerbation after ICS withdrawal.
Results: Higher sputum % eosinophils, higher sputum MPO/neutrophil level, longer duration of COPD symptoms, $<$40 packyears smoking, and ICS withdrawal in November, December or January were significant hazards (all $p < 0.05$) for experiencing a COPD exacerbation after ICS withdrawal in a monovariate model. In a multivariate model, all factors proved independent predictors except for sputum MPO/neutrophil level.

☆ This study has been registered at http://www.clinicaltrials.gov, ID: NCT00239278.

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Conclusions: Decisions on whether or not inhaled corticosteroids can be safely withdrawn in mild-to-moderate COPD can be facilitated by assessment of sputum inflammation, particularly eosinophil numbers, next to packyears smoking, season, and duration of COPD symptoms.

Introduction

Maintenance therapy with inhaled corticosteroids (ICS) in COPD is extensively debated. Virtually all studies have shown that ICS reduce exacerbation frequency in certain patients.[1,2] The current guideline of the "Global initiative for chronic Obstructive Lung Disease" (GOLD) recommends ICS therapy in COPD patients with a post-bronchodilator forced expiratory volume in one second (FEV_1) <50%predicted (GOLD stage III/IV) and repeated exacerbations.[1] In contrast to the GOLD-guidelines, many patients with mild-to-moderate COPD (GOLD stage I/II) also use ICS on a daily basis.[3] Additionally, there is reluctance to take patients off ICS who are already using them, which is likely linked to the experience that exacerbations occur frequently after stopping corticosteroids. This clinical notion of the difficulty to stop ICS in a substantial subgroup of COPD patients is now supported by at least two randomized trials investigating the effects of ICS withdrawal.[4,5]

The long-term use of ICS is associated with adverse effects and marked costs. If indeed some patients can do well without continuing their inhaled corticosteroid use, while others will do worse, it would be of great value to be able to estimate an individual's future exacerbation risk after stopping ICS. To our knowledge, no study so far has investigated the role of inflammatory parameters as a risk factor for an ensuing exacerbation after ICS withdrawal, though Siva et al have shown that COPD patients with sputum eosinophilia could reduce exacerbation frequency by inhaled steroids.[6] Therefore, we expected that especially higher sputum eosinophil percentages are a hazard for clinical deterioration.

To address the issue of prediction of exacerbations after ICS withdrawal we performed a study in which we discontinued ICS and searched for predictors of early exacerbations. Airway inflammation, patient characteristics, lung function, and health status were assessed in stable COPD patients before ICS withdrawal. After ICS withdrawal, time to exacerbation was assessed. We hypothesized that COPD patients with more active airway inflammation before ICS withdrawal are at increased risk for exacerbations.

Methods

Subjects

Smokers and ex-smokers with a diagnosis of COPD were included if on inhaled corticosteroid maintenance therapy, aged above 40 years, with a post-bronchodilator FEV_1 below 85% of predicted but above 0.7 l, and with a post-bronchodilator FEV_1/inspiratory vital capacity (IVC) below predicted (<88% predicted in men and <89% predicted in women). Patients with a history of asthma, using long-term oxygen therapy, or with significant other disease that could influence the results of the study were excluded. The use of oral corticosteroids was not allowed from 4 weeks before inclusion. The local medical ethics committee approved the study. A written informed consent was obtained from all patients prior to the study.

Study design

This manuscript presents the analysis of the period from study enrolment to the time of the first exacerbation. When patients exacerbated, a randomized controlled trial was conducted which is reported separately.[7]

At the enrolment visit, medical history was taken and a physical examination was performed. In addition spirometry and body plethysmography were performed, followed by sputum induction, quality of life questionnaires, blood, and urine sampling. At the end of this visit ICS were discontinued and the time to exacerbation was monitored. Because of the above mentioned ensuing randomized controlled trial, long-acting β_2-agonist were changed to short-acting β_2-agonists two months after enrolment. Patients were instructed to contact the investigators when pulmonary symptoms occurred or deteriorated. An exacerbation was defined according to the definition of Davies et al., i.e. increased breathlessness and at least two of the following symptoms for 24 h or more: increased cough frequency or severity, increased sputum volume or purulence, and increased wheeze,[8] requiring extra prednisolone and/or antibiotics after ICS discontinuation as judged by a medical doctor.

Measurements

At the enrolment visit, post-bronchodilator spirometry and bodyplethysmography (Jaeger Pneumotachograph/Masterscreen body, VIASYS Healthcare Inc, Conshohocken, USA) were performed after inhalation of 400 μg salbutamol according to ERS standards.[9] Directly after the lung function measurements, a sputum induction was performed with nebulised 4.5% sodium chloride solution for 3 × 5 min, with modifications when FEV_1 was below 1.5 l.[10] Subsequently blood and urine samples were collected. Finally, health status was assessed by the Chronic Respiratory Questionnaire (CRQ),[11] and the Clinical COPD Questionnaire (CCQ).[12] Higher scores in the CRQ represent better health status, while higher scores in the CCQ represent worse health status.

Sputum processing

The whole sputum sample was processed. Differential cell counts were performed and soluble mediators were measured in sputum supernatant by ELISA: leukotriene-B4 (LTB4), eosinophilic cationic protein (ECP), and myeloperoxidase (MPO) (see online supplement).

Sputum cytokine mRNA expression

For more details, see online supplement. In short, messenger ribonucleic acid (mRNA) was harvested from 1x 10^6 non-squamous sputum cells. Expression of cytokine mRNA was analysed for haemoxygenase-1 (HO-1), tumour necrosis factor alpha (TNF-α), regulated on activation, normal T-cell expressed and secreted (RANTES), interleukin 5 (IL-5), IL-10, IL-12, IL-13, transforming growth factor-β (TGF-β), interferon-γ (IFN-γ), and β_2-microglobulin were analysed by quantitative real-time PCR (see online supplement). Cytokine gene expression was normalised to β2-microglobulin expression. The mRNA quantification is expressed in threshold cycle (Ct) values, which is the number of amplification cycles to reach a detectable mRNA amount. Thus lower Ct-values correspond with higher mRNA expression. These values were available for 46 subjects, because it was added to the protocol later.

Blood and urine analyses

Methods for determination of blood differential cell counts, C-reactive protein (CRP), soluble intercellular adhesion molecule (sICAM), and urine desmosine are presented in the online supplement.

Statistics

Baseline characteristics are presented as medians (interquartile range). Continuous variables were tested for linearity with time-to-exacerbation. Non-linearly related variables were logarithmitised, tested again, and otherwise dichotomised using the median values as cut-off. Monovariate Cox regression analyses were performed using patient characteristics, lung function, sputum, urine, blood, and health status parameters to identify significant hazards of experiencing a COPD exacerbation after ICS discontinuation. The survival variable used was "time to exacerbation", defined as the time to the first exacerbation. The survival variable was censored, that is, it contains survival times and patients not experiencing an exacerbation before the end of the study. Multivariate Cox regression analysis was used to adjust survival comparisons for potential confounders, using the factors with a p-value <0.10 from the monovariate analyses. Kaplan–Meier curves were used to compare survival in subpopulations defined by medians of a single variable. Correction for the effect of seasonality on exacerbation prediction was done after inspecting plots, by defining a dichotomous variable indicating withdrawal in November, December or January, as opposed to outside those three months. A p-value <0.05 was considered to be significant.

Results

Baseline characteristics

Sixty-eight of the 114 screened patients with COPD were included between January 2001 and January 2005. The main reasons for exclusion were failure to meet the inclusion criteria (not-using ICS, cardiovascular instability, and lung function criteria) and inability to produce an adequate sputum sample at visit 1. The 68 included patients were monitored for a median (interquartile range) time of 146 (75–357) days. Fifty-four patients experienced an exacerbation, after a median time of 132 (70–214) days. The baseline characteristics of the patients included in the current analyses are presented in Table 1, and their inflammatory parameters in Table 2.

Monovariate Cox regression analyses

Baseline characteristics

Duration of COPD symptoms (duration of COPD) was a significant demographic risk factor for developing a COPD exacerbation after ICS withdrawal (Hazard ratio (HR) 1.07, $p = 0.001$, Table 3). Season of ICS withdrawal (November, December, or January) also proved to be a hazard (HR 4.2, $p < 0.001$). Packyears was dichotomised using the median value (40). Having smoked <40 packyears was a predictor for developing an exacerbation (HR 0.54, $p = 0.03$). None of the other baseline values such as age, gender, current smoking, body mass index, daily dose of ICS, and blood

Table 1 Baseline clinical and demographic characteristics.

Number of patients	68	
Number of exacerbations	54	
Gender (m/f)	53/15	
	Median	25–75 percentile
Age (years)	64.2	58.6–70.6
Packyears smoking	40.0	28.5–51.8
BMI (kg m^{-2})	26.3	23.9–28.6
Daily dose of ICS (μg)	800	500–1000
Post-bronchodilator lung function		
FEV_1 (L)	1.84	1.41–2.24
FEV_1 (%pred)	63.0	50.7–75.4
FVC (%pred)	100.0	90.5–106.0
IVC (%pred)	104.2	93.4–115.5
FEV_1/IVC	0.47	0.38–0.55
sGAW (kPa s)$^{-1}$	0.67	0.45–1.02
TLC (L)	7.63	6.71–8.38
TLC (%pred)	114.7	105.8–126.9
ITGV (%pred)	133.8	116.2–151.5
RV (%pred)	146.8	125.4–164.4
ITGV%TLC (%pred)	108.7	101.5–115.1
RV%TLC (%pred)	116.3	104.2–128.5
Health status-Chronic Respiratory Questionnaire		
Total score	19.4	17.4–21.6
Health status-COPD Control Questionnaire		
Total score	2.00	1.40–2.58

All variables are expressed as median, interquartile range. BMI, body mass index; ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IVC, inspiratory vital capacity; sGAW, specific airway conductance; TLC, total lung capacity; ITGV, intra-thoracic gas volume; RV, residual volume; IC, inspiratory capacity.

Table 2 Baseline inflammatory characteristics.

	Median	25–75 percentile
Sputum cells		
Total cell count ($\times 10^6$/ml)	5.37	2.26–13.5
Viability (%)	85.3	77.6–92.4
Eosinophils[a] (%)	1.60	0.50–3.73
Neutrophils (%)	72.7	62.3–81.5
Macrophages (%)	18.6	13.4–29.7
Lymphocytes (%)	0.70	0.20–1.50
Sputum supernatant proteins		
ECP (μg/l)	151	56–420
ECP/eosinophils (μg/10^9 cells)	1423	583–3276
MPO (μg/ml)	12.3	6.57–40.8
MPO/neutrophils(μg/10^6 cells)	3.70	1.67–8.17
LTB_4 (ng/ml)	0.49	0.28–1.17
Sputum mRNA. Ct-values. $N = 47$		
RANTES	28.9	28.4–29.6
IL-5	41.1	37.3–42.9
IL-10	29.8	29.2–30.5
IL-12a	41.9	38.1–42.9
IL-12b	41.0	37.0–42.8
IL-13	41.0	36.5–42.6
IFN-γ	34.2	32.9–35.1
TGF-β	25.7	24.7–26.2
TNF-α	26.5	26.1–27.4
Haemoxygenase-1	25.5	25.1–26.1
Serum		
CRP (mg/l)	3.36	1.85–7.51
sICAM (ng/ml)	115.3	95.4–155.8
Urine		
Desmosine (mM/mmol creatinine/l)	15.7	8.90–25.3

All variables are expressed as median, interquartile range. ECP: eosinophilic cationic protein; MPO, myeloperoxidase; LTB_4, leukotriene-B_4; CRP, C-reactive protein; sICAM, soluble intercellular adhesion molecule; RANTES, regulated on activation; normal T-cell expressed and secreted; IL, interleukin; IFN-γ, interferon-gamma; TNF-α, tumour necrosis factor-alpha; TGF-β, transforming growth factor-beta; Ct-values, cycle threshold values, which is the number of amplification cycles to reach detectable mRNA amount, normalised for β2-microglobulin expression. Lower Ct-values correspond with higher mRNA expression.

[a] Sputum eosinophils were <3% in 47 out of 68 subjects.

pressure were significant risk factors in the monovariate Cox regression analyses. Similarly, health related quality of life as determined by CRQ or CCQ was not predictive of time to exacerbations. For a table with all characteristics tested, see online Supplementary Table E1.

Lung function

None of the lung function parameters reflecting airway obstruction (FEV_1, FVC, FEV_1/FVC, sGAW) or hyperinflation (TLC, RV, FRC, FRC%TLC, ITGV%TLC) were statistically significant risk factors of the time to exacerbation in a monovariate model. When the severity of airway obstruction was categorised by GOLD stage, this too was not predictive of an exacerbation (Supplementary Table E1).

Table 3 Significant monovariate Cox regression hazard ratios for time to exacerbation.

	Hazard ratio	95% CI	*p*-Value
Packyears smoking ≥ 40[b]	0.54	0.31–0.93	0.03
Durations of symptoms (years)	1.07	1.03–1.11	0.001
ICS cessation in November, December or January[c]	4.16	2.02–8.57	<0.001
% sputum eosinophils[a]	1.42	1.10–1.83	0.007
Serum MPO (μg/10^6 neutrophils)[a]	1.36	1.08–1.71	0.01
Serum CRP (mg/l)[a]	0.79	0.61–1.02	0.065

[a] Logarithmitised.
[b] Dichotomised using the median value at baseline.
[c] Dichotomised as "in" versus "outside" the period.

Inflammation

Sputum eosinophil percentage was a significant hazard for developing an early COPD exacerbation (HR 1.42, $p = 0.007$, Table 3). In a prior study, ICS treatment showed to be most beneficial in COPD patients with a baseline sputum eosinophil count above 3%.[6] Therefore, % sputum eosinophils were also tested as a dichotomous variable (≥3% versus <3%) in the survival analysis. Subjects with more than 3% sputum eosinophils had a significantly increased risk for earlier development of an exacerbation compared to subjects with lower percentages of sputum eosinophils (Fig. 1). Neutrophils, macrophages, and lymphocytes were not predictive of an exacerbation, neither expressed as cell numbers nor as % of total sputum

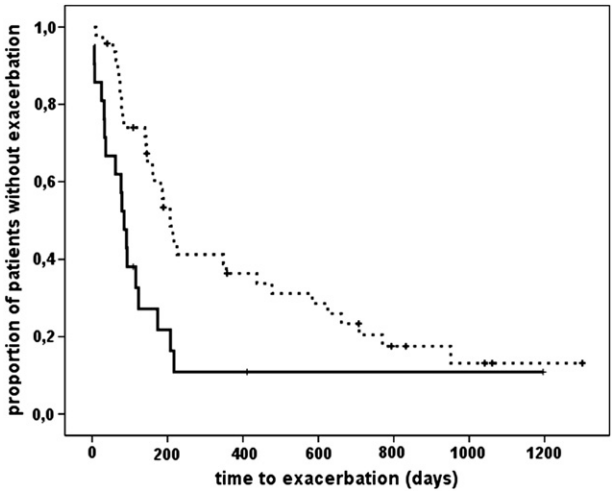

Figure 1 Kaplan-Meier plot of risk of exacerbation in subjects with ≥3.0% sputum eosinophils (solid line) and subjects with <3.0% sputum eosinophils before ICS withdrawal (dotted line) ($p = 0.005$).

cell count. Sputum MPO level per neutrophil was a significant hazard for experiencing an exacerbation (see Table 3), but not sputum MPO level per se, nor sputum ECP level, ECP per eosinophil, and LTB_4. The hazard ratio of serum CRP was 0.79, and just failed to be significant ($p = 0.065$). The hazard ratios of mRNA-levels for RANTES, IL-5, IL-10, IL-12a, IL-12b, IL-13, TGF-β, TNF-α, and IFN-γ did not reach statistical significance, nor did the hazard ratios of soluble ICAM levels, and urinary desmosine (corrected for creatinine) (Supplementary Table E1).

Multivariate analyses

All factors with a *p*-value below 0.10 in the monovariate analyses were included in a multivariate model (see Table 3). Percentage sputum eosinophils, longer duration of COPD symptoms, less than 40 pack years smoking, and season of inclusion proved to be independent predictors for experiencing a COPD exacerbation after ICS withdrawal (Table 4). Using the variable $\geq$3% sputum eosinophils instead of % sputum eosinophils did not change the results.

Discussion

This study shows that sputum eosinophilia, the duration of COPD symptoms and smoking habits, and season are predictive for an earlier exacerbation in patients with mild-to-moderate stable COPD when indiscriminately taken off their inhaled corticosteroids.

According to the GOLD guidelines, many patients who are currently treated with ICS should in fact not be using them. Thus doctors should withdraw ICS from these patients. However, in practice, this poses marked problems in some patients. Predictors to assess the patient's exacerbation risk would be helpful for clinicians to aid in deciding whether or not to discontinue ICS therapy. Although many patient characteristics have been identified that are associated with an increased risk of developing a COPD exacerbation[13–27] to our knowledge no study has been published in which inflammatory parameters were evaluated as risks for exacerbation after ICS discontinuation.

Table 4 Multivariate Cox regression hazard ratios for time to exacerbation.

	Hazard ratio	95% CI	*p*-Value
Packyears smoking $\geq$ 40[b]	0.57	0.32–1.00	0.05
Durations of symptoms (years)	1.06	1.02–1.10	0.003
ICS cessation in November, December or January[c]	3.61	1.67–7.79	0.001
% sputum eosinophils[a]	1.34	1.04–1.71	0.02
Serum MPO ($\mu g/10^6$ neutrophils)[a]	1.18	0.90–1.53	0.23
Serum CRP (mg/l)[a]	0.79	0.58–1.07	0.12

[a] Logarithmitised.
[b] Dichotomised using the median value at baseline.
[c] Dichotomised as "in" versus "outside" the period.

In our study, percentage of sputum eosinophils, assessed in a stable phase of the disease while patients were still using ICS therapy, was a significant predictor for development of an earlier COPD exacerbation after ICS discontinuation. It has been suggested previously that the numbers of eosinophils[28–31] and their chemo-attractants[32,33] are increased during COPD exacerbations. Sputum eosinophilia can be present in stable disease and more importantly, we now demonstrate that increased eosinophil percentages predict a shorter time to exacerbation after discontinuation of ICS. Additionally, previous studies have shown that especially COPD patients with an eosinophilic inflammatory pattern in their sputum benefit most from ICS maintenance therapy[32] and from oral corticosteroids during stable COPD.[34] This is in line with the fact that the eosinophil is a very steroid-sensitive cell type.

Siva et al. have recently reported a study in which steroid maintenance treatment based on sputum eosinophil levels resulted in a decrease in severe exacerbation rates.[6] Our finding that patients with higher percentage of sputum eosinophils (before ICS withdrawal) are at an increased risk for developing a COPD exacerbation after ICS withdrawal is fully compatible with their study. From their study and our findings, we conclude that it might be problematic to withdraw ICS in patients with higher eosinophil levels for trial purposes, and less desirable in the clinical setting. Our data suggest that a decision to discontinue the ICS should be made on the sputum eosinophil percentage. Subjects with more than 3.0% eosinophils should probably not discontinue their ICS because their chance of experiencing an exacerbation is markedly higher. It would now be timely to perform a prospective study in patients with COPD in whom discontinuation of inhaled corticosteroids is considered dependent on the sputum eosinophil percentage.

COPD has traditionally been regarded as disease with a major neutrophilic component. Neutrophil numbers were not a significant risk factor for earlier COPD exacerbation after ICS discontinuation. Since corticosteroids are less effective in reversing neutrophilia than eosinophilia,[34] we did not expect that the presence of higher numbers of neutrophils would constitute a high risk for exacerbations specifically after ICS withdrawal. Sputum neutrophil numbers could have proven, however, to be predictive of increased exacerbation risk *independent* of ICS withdrawal, but this was not the case in our study. Monovariate Cox proportional hazard survival analysis showed that neutrophil activation as assessed by the level of MPO/neutrophil in sputum was related to the development of an exacerbation, but the significance was lost in the multivariate model. One of the main functions of MPO is its antibacterial effect. MPO levels are highly correlated with bacterial load in bronchoalveolar lavage in a combined group of patients with stable obstructive and non-obstructive chronic bronchitis.[35] Furthermore, MPO levels are significantly higher in patients with higher bacterial load in their sputum during an exacerbation.[36] Thus, it is possible that the activation level of neutrophils in our patients reflects bacterial colonisation of the airways more than a trait amenable to steroid effects.

Low serum CRP levels tended to be a risk factor for development of a COPD exacerbation after ICS withdrawal in the monovariate model. Former studies in COPD showed

that oral and inhaled corticosteroids reduce[37] and ICS withdrawal raises CRP levels.[38] We postulate that low CRP levels may reflect effective control of airway inflammation in COPD patients on ICS, and that ICS withdrawal leads more easily to an exacerbation especially in these patients.

Sputum cytokine mRNA levels (IL-5, IL-10, IL-12a+b, IL-13, TNF-α, TGF-β, and IFN-γ) did not identify persons at risk for developing a COPD exacerbation after ICS withdrawal in our sub-study of 46 patients with mRNA determinations. We can not rule out that the use of inhaled corticosteroids by our subjects might have contributed to this. Alternatively, this may also imply that mRNA is not an optimal way to assess the potential of measuring cytokines and mediators in a pending exacerbation after ICS withdrawal, or that our number of patients was too low to address this issue, or that there were technical issues not yet indentified by us. Further studies clearly have to replicate this, as well as extend our observations to the protein level.

Perhaps the most remarkable finding is that the level of FEV_1 was *not* predictive of the time to exacerbation in patients with mild-to-moderate COPD. In the much larger, recently published data from the Eclipse study [25], a lower FEV_1 was associated with a higher risk of being a frequent exacerbator, but there were marked numbers of patients with frequent exacerbators also in patients with an FEV_1 between 50 and 80% predicted (GOLD 2). The emphasis in the current guidelines[1] to only prescribe ICS to patients with an FEV_1 below 50% predicted in combination with an increased exacerbation frequency should be re-evaluated.[1] It remains, however, totally logic not to prescribe ICS to reduce the number of exacerbations in patients who do not experience any exacerbation, but uncoupled from GOLD stage. Indeed the study in the literature (Jones et al.) on which this criterion of only prescribing ICS to patients with an FEV_1 was based,[39] found a larger absolute reduction in exacerbation frequency in patients with an FEV_1 above 50% predicted than below 50%. However, the reduction in exacerbation frequency was only significant in the group of patients with an FEV_1 below 50% predicted.

Time since onset of COPD symptoms was also a significant predictor of increased risk of exacerbations when ICS were discontinued. This duration of COPD was predictive for exacerbations and hospitalizations in one previous larger study.[14] Unfortunately, we do not have data on prior exacerbation frequency, which in the Eclipse study proved to be the best predictor of future exacerbation frequency.[25] None of the other baseline characteristics, lung function or health status parameters, turned out to be significant predictors in our study. Numerous other non-inflammatory risk factors for (hospitalization due to) exacerbations have been found in previous studies.[13–20] These observational studies were usually in larger cohorts of hospitalised patients. We are aware that our study may have included a too small number of patients to find some of the above-mentioned hazards for exacerbations. However, our significant result with eosinophils was already apparent in a study with only a low sample size and may underline the importance of sputum inflammation.

Opposite to what we had expected, smoking more than 40 packyears was a protective factor for developing a COPD exacerbation after ICS withdrawal. We speculate that a healthy smoker effect is responsible for this finding, which means that patients who do not tend to exacerbate can keep on smoking and that withdrawal of ICS does not change this tendency.

The multivariate model was corrected for seasonal effects by including a factor on whether ICS withdrawal occurred in November, December, or January. This season had a significant hazard ratio of 3:5. This seasonal effect was expected because periods with high frequency of COPD exacerbations parallels periods with high incidence of respiratory viruses.[40] After correction of the seasonal influence, % sputum eosinophils, duration of COPD symptoms, and packyears smoking remained independent predictors of time to exacerbation in the multivariate model. Although perhaps not unexpected, we believe this is the first study to document that discontinuation of ICS in November, December, or January poses increased risks of exacerbations.

We conclude that assessment of sputum inflammation can aid the physician to decide which COPD patient using ICS can actually stop this treatment outside the exacerbation season without increased risk of an early exacerbation. Sputum eosinophilia is the most informative inflammatory parameter in this respect, and to a smaller extent neutrophil activation. Independent other predictors were packyears smoking and duration of symptoms. We suggest that the evaluation of sputum eosinophilia greater than 3% can be employed prospectively for a treatment decision with respect to discontinuation of inhaled corticosteroids in patients with mild-to-moderate COPD.

Conflict of interest

None to declare.

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Declaration

The local medical ethics committee approved the study. A written informed consent was obtained from all patients prior to the study. The study was performed according to the declaration of Helsinki.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2011.07.002.

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