Blood eosinophil count to predict bronchial eosinophilic inflammation in COPD

To the Editor:

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the airways. There is evidence that maintenance treatment with inhaled corticosteroids (ICS) in COPD results in a reduction in the mean rate of exacerbations, and improvement in quality of life and lung function [1]. However, ICS therapy has been associated with increased risk of oropharyngeal candidiasis, hoarseness and pneumonia [1]. In COPD, ICS are now recommended in cases of frequent exacerbations and severe obstruction [2].

Even if neutrophilic inflammation is conspicuous in the airways of most COPD and related to the severity of airway obstruction [3], some patients may exhibit raised airway eosinophilic inflammation [4, 5], and those patients show the greater response to a short course of oral [4] and inhaled corticoids [6]. A strategy that focused on sputum eosinophils to adjust dose of ICS and oral glucocorticoids in COPD proved to reduce exacerbation and hospitalisation [7]. Given the difficulty of applying the technique of induced sputum in clinical practice, there is a need to find a biomarker to identify sputum eosinophils in COPD, as has been done in asthma.

Raised blood eosinophil count is a common finding in COPD (37.4% with persistent blood eosinophil count ≥2%) [8] and seems a promising biomarker to predict the response of COPD patients to ICS [9, 10]. Furthermore, blood eosinophil count ≥2% during an exacerbation was found to predict the utility of systemic corticoids to accelerate recovery [11]. Likewise, this threshold predicted that chronic treatment with ICS added to long-acting β-agonists (LABA) would prevent exacerbation [9]. Clinical benefit from maintenance treatment with ICS in COPD has recently been found to be particularly clear when the blood eosinophil count was >280 per μL [10].

In contrast to asthma, there are no data in the literature on the ability and thresholds of blood eosinophil count to reflect bronchial eosinophilic inflammation in COPD.

We conducted a retrospective study of 155 consecutive COPD patients seen at the COPD clinic of a university hospital (CHU Sart-Tilman, Liege, Belgium), where COPD was defined as a post-bronchodilation forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio <70%. Patients filled in the COPD Assessment Test (CAT) questionnaire and underwent exhaled nitric oxide fraction (FeNO) measurement followed by spirometry, sputum induction and blood sampling on the same day during a 1-h visit. Data are
155 patients aged 61±10 years, of whom 104 were males, 43% current smokers and 52% ex-smokers. Median (IQR) post-bronchodilator FEV\textsubscript{1} and FEV\textsubscript{1}/FVC were found to be 56% (52-62%) predicted and 53% (48-55%), respectively. CAT score was 21 (6-34) with 97% of patients having a score ≥10. Blood eosinophils were 160 (135-187) μL or 2% (1.7-2.3%). Sputum eosinophil and neutrophil counts were 1.4% (1–3%) and 71.3% (66-76%), respectively. 58 (37%) out of 155 patients had >3% sputum eosinophils. F\textsubscript{E}NO was 17 (15–19) ppb and total serum IgE was 79 (52–130) kU·L\textsuperscript{-1}. In our population, 29% were steroid naïve, 15% were treated with low doses of ICS, 24% with moderate doses of ICS and 32% with high doses of ICS. 5% were treated with chronic oral corticosteroids. 75% received long-acting β\textsubscript{2}-agonists while 50% received long-acting antimuscarinic agents.

In patients receiving high doses of ICS (n=50), the median blood eosinophil count was 207 μL. The best cut-off value of blood eosinophil count for the prediction of sputum eosinophil count ≥3% in this group was 215 μL (AUC 0.76, p=0.001, 60% sensitivity, 93% specificity) or 2.3% (AUC 0.78, p<0.0001, 62% sensitivity, 94% specificity).

We found a lower utility of F\textsubscript{E}NO for the prediction of uncontrolled sputum eosinophilic inflammation in COPD patients (cut-off 24 ppb; AUC 0.65, p=0.004, 38% sensitivity, 91% specificity). Looking specifically at non-smokers, the ROC curve identified a F\textsubscript{E}NO level >24 ppb as the best cut-off point, giving 42% sensitivity and 82% specificity (AUC 0.6) in predicting sputum eosinophil count ≥3%. There was a poor, though significant, correlation between F\textsubscript{E}NO and sputum eosinophil count in COPD (r\textsubscript{s}=0.32, p=0.001). By contrast, serum total IgE levels had no ability to discriminate between those with eosinophilic and noneosinophilic COPD (AUC 0.55, p>0.05). Next, we looked at combined F\textsubscript{E}NO and blood eosinophils as predictors of sputum eosinophilia. When comparing AUCs in the three models (F\textsubscript{E}NO versus blood eosinophils versus F\textsubscript{E}NO plus blood eosinophils) (figure 1), combining F\textsubscript{E}NO and blood eosinophils did not improve the prediction of sputum eosinophilia (AUC 0.77) compared to blood eosinophils alone.

There are no data in the literature on the blood eosinophil thresholds predicting bronchial eosinophilic inflammation in COPD. Here, we provide thresholds in a population of stable COPD and in a subpopulation of COPD patients treated with high doses of ICS. In a population of 155 stable COPD patients, we found that the best cut-off values of blood eosinophil counts to identify a sputum eosinophil count ≥3% are 162 μL or 2.6%. When focusing on COPD patients treated with high doses of ICS, the best cut-off points were 215 μL or 2.3%. F\textsubscript{E}NO was able to discriminate between eosinophilic and noneosinophilic inflammation but with lesser accuracy than that previously observed in asthma [13]. The best F\textsubscript{E}NO threshold was also lower in COPD (24 ppb) than that found in asthmatics (42 ppb) [13]. By presenting as mean±SD or mean±SEM for continuous variables; median (interquartile range (IQR)) was preferred for skewed distributions. For categorical variables, the number of observations and percentages are given in each category. By constructing receiver operating characteristic (ROC) curves, we identified a blood eosinophil count cut-off point, either taken as a percentage or as absolute value, for identification of sputum eosinophil count ≥3%, in stable COPD patients and in a subpopulation treated with high doses of ICS (inhaled propionate fluticasone ≥500 μg per day). We also looked at the prediction of sputum eosinophilic inflammation using F\textsubscript{E}NO and total IgE levels as we previously showed those factors to be good predictors of sputum eosinophilia in asthmatics [12]. The protocol was approved by the Hospitalo-Facultaire Universitaire ethics committee, Liege (institutional review board 2005/181).
contrast, total serum IgE level was unhelpful in identifying sputum eosinophilia. FeNO did not add value to blood eosinophil count in improving the prediction of sputum eosinophilia.

It is noteworthy that the blood eosinophil thresholds we report here as predicting sputum eosinophilia are very close to those recently shown to predict ability of ICS to prevent exacerbations when combined with LABA in stable COPD in large retrospective study [9].

We think that blood eosinophil counts should be useful to initiate ICS in COPD patients and to adjust ICS dose in those with recurrent exacerbations. Therefore, we believe our data are relevant for the numerous clinicians who have no access to induced sputum analysis, even though we are aware that the thresholds we propose here need to be validated in large-scale prospective studies.

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Blood eosinophil counts, but not FeNO, may predict airway eosinophilic inflammation

http://ow.ly/WXgkA

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