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Diagnosing persistent blood eosinophilia in asthma with single blood eosinophil or exhaled nitric oxide level

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ABSTRACT

Background: Eosinophilic asthma is characterized by persistently elevated blood eosinophils, adult-onset asthma and corticosteroid resistance. For stratified medicine purposes one single measurement of blood eosinophils or exhaled nitric oxide (FeNO) is commonly used. The aim of this study was to investigate in patients with new-onset asthma whether persistent blood eosinophilia can be predicted with one single measurement of these biomarkers.

Methods: Blood eosinophils and exhaled nitric oxide levels were measured at yearly intervals over 5 years in 114 adults with new-onset asthma on inhaled corticosteroid treatment. Two definitions of persistent blood eosinophilia were used (1); blood eosinophils at every visit $\geq 0.30 \times 10^9$/L, or (2) $\geq 0.40 \times 10^9$/L. Receiver operating characteristic analyses were performed. Diagnostic cut-off values were defined at a positive predictive value of 95% (or the highest achievable).

Results: Using definition 1 (blood eosinophils $\geq 0.30 \times 10^9$/L) the cut-off value for a single measurement of blood eosinophils was 0.47×10^9/L. For definition 2 ($\geq 0.40 \times 10^9$/L) the cut-off value was 0.49×10^9/L. Cut-off values for persistently low blood eosinophils were 0.17×10^9/L for definition (1) and 0.21×10^9/L for definition (2), respectively. For FeNO no cut-off values with sufficient accuracy could be defined.

Conclusion: We showed that by using high and low cut-off values, one single measurement of blood eosinophils, but not FeNO in the initial phase of new-onset asthma in adults can be used to predict persistence or absence of blood eosinophilia in asthma.

1. Introduction

Asthma is a heterogenic disorder with several distinct phenotypes, which are generally based on clinical, functional or inflammatory characteristics [1–6]. One important phenotype is severe eosinophilic asthma, defined by elevated levels of eosinophils in the airways or in blood despite treatment with medium to high dose inhaled corticosteroids and long-acting beta-agonists [7,8]. This is an important phenotype because it is characterized by poor symptom control, fixed airflow limitation and frequent exacerbations [9].

New biological agents targeting interleukin (IL)-5, a key interleukin in the pathway of eosinophilic inflammation, are able to reduce the exacerbation rate in these patients and also increase their quality of life [10–12]. This provides new treatment options for this severe asthma phenotype. It is therefore important to identify patients with this specific phenotype in an early stage of the disease, before severe exacerbations and loss lung function occur.

In clinical trials, single blood eosinophil or fraction of exhaled nitric oxide (FeNO) levels are commonly used to identify patients with the eosinophilic phenotype [7,11]. However, it remains highly questionable whether one single measurement of these biomarkers is adequate to diagnose the eosinophilic asthma phenotype.

In this study we selected adults with recent onset asthma to investigate whether a single measurement of blood eosinophils or FeNO could predict the eosinophilic asthma phenotype, thereby assuming that persistent blood eosinophilia precedes the development of this severe phenotype. For clinical practice we also defined cut-off values.

2. Methods

2.1. Subjects

The present study was part of the ADONIS-project (Adult-onset asthma and inflammatory subphenotypes) in which adults with recently

Abbreviations: AUC, area under the curve; CI, confidence interval; FeNO, fraction of exhaled nitric oxide; IL, interleukin; NPV, negative predictive value; PPV, positive predictive value; ROC, Receiver operating characteristic curve

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diagnosed asthma were included. For this study 358 patients were approached, of which 200 agreed to participate. There was no difference in patient characteristics between participants and non-participants except for gender (56% vs 70% females, respectively, $p < 0.01$). Asthma was diagnosed < 12 months before inclusion and based on typical asthma symptoms, combined with documented reversibility in FEV_1 of 12% predicted and 200 ml in absolute values, or presence of airway hyperresponsiveness [13]. Patients with a history of chronic airway disease in childhood were excluded. (Ex)smokers with > 10 pack years of smoking had to have $FEV_1/FVC > 0.7$ and normal diffusing capacity of the lungs for carbon monoxide (> 80%). The study was approved by the AMC Medical Ethics Board and registered in the Dutch trial register (NTR1846). All participants gave written informed consent.

2.2. Design and study procedures

In the ADONIS-project patients underwent an extensive assessment at baseline, and were invited to for reassessment at yearly intervals up to 5 years, and at one additional visit at 6 months. Peripheral blood cell counts and FeNO (NIOX System, Aerocrine, Sweden) [14] were collected at every visit, exacerbations, defined as a burst of oral corticosteroids, were reported and asthma control was assessed by the asthma control questionnaire (ACQ-6). Extensive assessments at baseline and at 4–5 years have been described previously [15] and included demographics, medical history, lung function measurement, atopic status, and nasal endoscopy. Differential cell counts in induced sputum were assessed according to international guidelines [16].

2.3. Defining persistent blood eosinophilia

Blood eosinophilia was defined by threshold levels of either $\geq 0.30 \times 10^9$/L [8,9,12] or $\geq 0.40 \times 10^9$/L [17–20], as both values are frequently used in clinical and pharmaceutical asthma research. Persistent blood eosinophilia (hereafter: “eosinophilic asthma”) was defined by levels consistently above the threshold during follow-up. Absence of blood eosinophilia (hereafter: “non-eosinophilic asthma”) was defined by levels consistently below this threshold. Patients who could not be classified in one of these two groups were considered as “fluctuating”. Blood eosinophil levels measured < 2 weeks after an exacerbation were not included.

2.4. Statistical analysis

Patients with at least one reassessment over 5 years were included in the analysis. Patients were excluded if they did not use inhaled corticosteroids at baseline or were on maintenance oral corticosteroid therapy. Receiver operating characteristic curve (ROC) analysis was used to determine the diagnostic value of one single blood eosinophil or FeNO level at baseline to diagnose “eosinophilic” and “non-eosinophilic” asthma during follow-up. For both biomarkers the area under the curve (AUC) was calculated. Cut-off values were defined at a positive predictive value (PPV) of 95%, or in case this value couldn't be reached, the highest achievable PPV below 95%. Corresponding sensitivity, specificity and negative predictive value (NPV) and accuracy were calculated. In addition, cut-off points for predicting persistent sputum eosinophilia (≥3%) were calculated, but since we expected the number of patients capable of producing adequate sputum samples to be low, we did not choose sputum eosinophilia to be the primary outcome. Analyses were performed in SPSS version 24.0 (IBM SPSS, Chicago, Ill).

3. Results

Data from 114 patients could be used in the analysis (Fig. 1). When comparing these patients with those that were excluded, no differences in baseline characteristics were observed, except for a slightly higher body mass index and lower dose of inhaled corticosteroids in the latter group *(data not shown)*. The median (interquartile) number of visits was 5 (4–6), the number of visits per patient can be found in Fig. 1. Characteristics of the included patients are shown in Table 1.

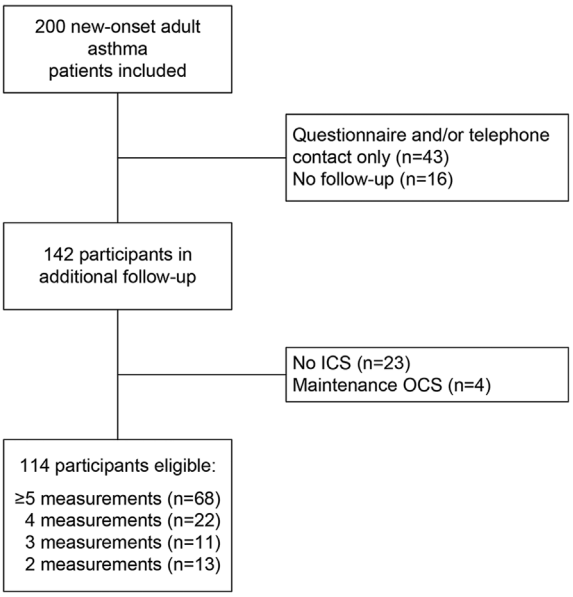

Fig. 1. Consort diagram. ICS; inhaled corticosteroids, OCS; oral corticosteroids.

3.1. “Eosinophilic asthma” defined by blood eosinophil threshold $\geq 0.30 \times 10^9$/L

Nine percent of the patients had persistent blood eosinophil levels $\geq 0.30 \times 10^9$/L at all visits, 72% had persistent blood eosinophils levels $< 0.30 \times 10^9$/L. Characteristics of these two groups as well as the group patients with fluctuating blood eosinophil levels are shown in Table 2. ROC analysis showed an AUC (95% Confidence Interval (CI)) of 0.89 (0.73–1.00) (Fig. 2a) for one single measurement of blood eosinophils to predict “eosinophilic asthma”. For FeNO the AUC was 0.73 (0.54–0.93) (Fig. 2a). The cut-off value of blood eosinophils for diagnosing “eosinophilic asthma” was $\geq 0.47 \times 10^9$/L with a PPV of 83%, and for FeNO ≥83 ppb with a PPV of only 40%. Cut off values for diagnosing “non-eosinophilic asthma” were $\leq 0.17 \times 10^9$/L eosinophils

Table 1
Baseline characteristics.

Subjects (n)	114	
Gender, % female	52	
Age (years)	49	± 14
BMI (kg/m^2)	28	± 5
Never/ex/current-smoker, %	40/54/5	
Pack Years	4	(0–14)
ACQ6-score	1.35	± 0.94
ICS dose, fluticasone equivalent (μg)[§]	500	(250–500)
Exacerbation (n in pervious year)	0	(0–1)
IgE	68	(28–201)
Atopy, %	43	
Nasal polyps, %	19	
postFEV_1 (% pred)	100	± 17
FeNO (ppb)	20	(13–40)
Blood eosinophils (x10^9/L)	0.17	(0.09–0.26)
Blood neutrophils (x10^9/L)	3.88	± 1.32
Sputum eosinophils (%) [¥]	0.70	(0.10–4.30)

Data are mean ± SD, median (interquartile range), or percentage. BMI, Body mass index; ACQ, asthma control questionnaire; ICS, inhaled corticosteroids; post, post-bronchodilator; FeNO, fraction of exhaled nitric oxide; ppb, parts per billion. [§]Reported daily dose, [¥]n = 86.