Predictors of frequent exacerbations in (ex)smoking and never smoking adults with severe asthma ☆

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ABSTRACT

Background: Persistent eosinophilic airway inflammation is an important driver for asthma exacerbations in non-smokers with asthma. Whether eosinophilic inflammation is also a predictor of asthma exacerbations in (ex)smokers is not known.
Objective: The aim was to investigate factors associated with frequent exacerbations in never smokers and (ex)smokers with asthma.
Methods: (Ex)smoking (n = 83) and never smoking (n = 70) patients with uncontrolled asthma despite high dose asthma medication (GINA treatment step 4–5) were selected from a cohort of 571 adult-onset asthma patients. Clinical, functional and inflammatory parameters were used in multivariate logistic regression analyses to identify factors associated with frequent exacerbations (≥3 oral corticosteroid (OCS) bursts in the previous year).
Results: Frequent exacerbations in (ex)smokers were independently associated with ICS dose (OR 1.2, 95%CI: 1.1–1.3) and blood neutrophil count (OR 1.5, 95%CI: 1.2–2.1). In never smokers frequent exacerbations were independently associated with blood eosinophil count (OR 18.9, 95%CI: 1.8–202.1).
Conclusion and clinical relevance: This study shows that never smoking and (ex)smoking patients with severe asthma have different predictors of frequent exacerbations: higher blood neutrophils in (ex) smokers *versus* higher blood eosinophils in never smokers. This suggests that different types of systemic background inflammation play a role in the aetiology of exacerbations in these patients.
Clinical trial registration: Netherlands Trial Register: NTR2217, NTR1846 and NTR1838.

1. Introduction

Asthma exacerbations impose a major burden on patients' lives and account for a large part of asthma related health care costs [1]. The importance of persistent eosinophilic airway inflammation in asthma exacerbations has been recognized for many years [2]. Increased levels of sputum eosinophils precede and predict exacerbations [3,4]. Adjusting anti-inflammatory treatment based on sputum eosinophil level has been shown to reduce asthma exacerbations [5,6]. Moreover, suppression of eosinophils with antibodies directed against interleukin (IL)-5 leads to a 50% reduction in exacerbation frequency [7,8]. However, in the majority of asthma studies only non-smoking patients were included [9]. Whether airway eosinophilia is also a predictor of asthma exacerbations in

current and exsmoking asthma patients is not known.

In the present study we hypothesized that airway eosinophilia is a predictor of asthma exacerbations in both never smokers and (ex) smokers. Therefore we investigated factors associated with frequent exacerbations in never smokers and (ex)smokers with asthma.

2. Methods

2.1. Study design and participants

This was a cross-sectional study using pooled baseline-data from three observational cohort studies with similar methodologies. These three studies included in total 571 patients with adult-onset asthma between 2009 and 2012 (Netherlands Trial Register numbers: NTR2217, NTR1846 and NTR1838) and aimed at phenotyping patients based on an extensive set of clinical, functional and inflammatory parameters. All three trials were reviewed and approved by medical ethical boards before their initiation.

Adult patients were eligible for the three cohorts if they had a confirmed diagnosis of asthma with onset of the disease after the age of 18 years. Asthma diagnosis was based on a history of variable respiratory symptoms AND documented variable expiratory airflow limitation: reversibility in FEV_1 of >12% predicted and 200 ml or airway hyperresponsiveness to inhaled methacholine (PC20 < 8 mg/ml) or diurnal variation in PEF of $\geq$20% or history of prompt deterioration in FEV_1 after $\leq$25% reduction in oral or inhaled corticosteroid dose (within 4 weeks) [1]. Patients with other pulmonary diseases, non-related major co-morbidities, and pregnancy were excluded. Smoking was allowed, however, patients with a smoking history of >10 pack years combined with fixed airflow obstruction and/or reduced diffusion capacity (DLCO/VA <80%) were excluded. Detailed in- and exclusion criteria have been reported previously [10—12]. All patients were informed and gave written consent.

For the present study patients with severe asthma were selected (see Fig. 1 for study flowchart); those using high intensity asthma treatment as defined by GINA treatment step 4—5 (use of high dose inhaled corticosteroid and a second controller or systemic corticosteroid use >50% of the previous year) [1] and with uncontrolled asthma defined as either asthma control questionnaire (ACQ)-score

>1.5, 2 or more exacerbation per year or presence of airflow limitation with an FEV_1 <80% predicted [13].

After that, patients were stratified according to smoking status: current smokers and ex-smokers were combined into one group called (ex)smokers [11], their smoking history was quantified by calculating the number of pack years. Never smokers were patients who had never smoked.

Finally, (ex)smokers and never smokers were divided in two groups: 3 or more exacerbations (frequent exacerbations) or $\leq$ 1 exacerbations in the previous year (non-frequent exacerbations) as previously reported [14,15]. An asthma exacerbation was defined as an increase in asthma symptoms requiring treatment with a course of oral corticosteroids (OCS) or at least a doubling from a stable maintenance dose for at least three days. Courses of systemic corticosteroid separated by one week or more were recorded as a separate exacerbation.

2.2. Assessments

2.2.1. Clinical parameters

Systematic medical history was taken with regard to asthma symptoms, including asthma-specific questionnaires (Asthma Control Questionnaire (ACQ) [16] and Asthma Quality of Life Questionnaire (AQLQ)) [17], medication use and asthma related healthcare consumption in the previous year (number of courses oral corticosteroids). Co-morbidities with possible influence on asthma symptoms were recorded; gastro-esophageal reflux disease, chronic rhinosinusitis (based on symptoms and combined with sinus CT-scan or nasal endoscopy if available).

2.2.2. Functional parameters

The following lung function measurements were performed according to international standards: spirometry (pre-bronchodilator and postbronchodilator FEV_1 and forced vital capacity (FVC)) [18], single breath carbon monoxide diffusing capacity of the lung (TLCOc/VA) [19], static lung volumes by bodyplethysmography (total lung capacity (TLC) and residual volume (RV)) [20] and airway hyperresponsiveness to methacholine (provocative concentration causing a 20% drop in FEV_1 (PC20)) [21].

2.2.3. Inflammatory markers

Fraction of exhaled nitric oxide (FeNO) was measured with a portable rapidresponse chemiluminescent analyzer (NIOX system, Aerocrine, Sweden) [22]. Venous blood was collected and differential white blood cell counts, total and specific IgE to common allergens (ImmunoCAP, Thermo Scientific, Uppsala, Sweden) measurements were performed. Atopy was defined as one or more specific IgE levels above 0.35 kU/L. Sputum induction and processing was done according to internationally accepted standards as described previously [23]. Results for different sputum cell types are presented as percentage of total non-squamous cell count.

2.3. Statistical analysis

First, characteristics of (ex)smokers and never smokers were compared. Second, (ex)smoking patients with and without frequent exacerbations and never smoking patients with and without frequent exacerbations were compared. Comparisons were made by either student t-test, Mann-Whitney U test or chi square, whenever appropriate.

In order to identify variables potentially associated with frequent exacerbations, all variables with a p-value <0.10 in the comparison between patients with and without frequent exacerbations in the (ex)smoker or never smoker group were used in a univariate logistic regression analysis. After that, variables with a p-
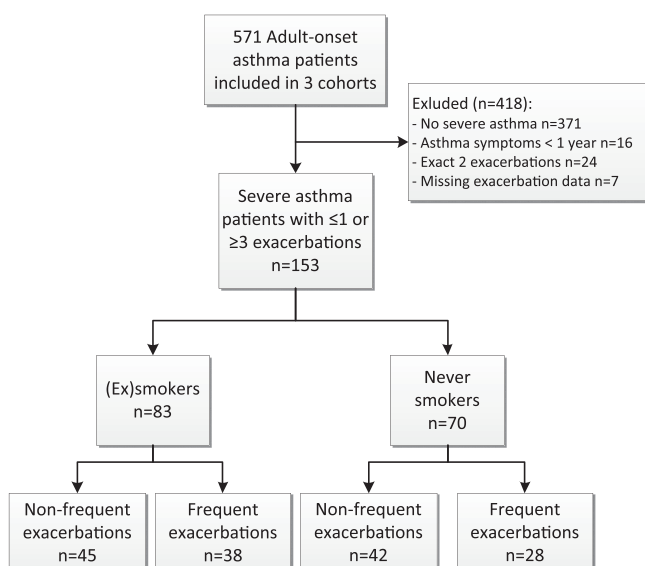

Fig. 1. Study flowchart.