Original Article

Asthma Control and Sputum Eosinophils: A Longitudinal Study in Daily Practice

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What is already known about this topic? There is strong evidence in the literature that sputum eosinophilic inflammation is related to the risk of asthma exacerbations. However, the relationship between eosinophilic inflammation and asthma control has been less firmly established.

What does this article add to our knowledge? This longitudinal study confirms the relationship between asthma control and sputum eosinophils in daily practice and is the first to propose a minimal important difference of sputum eosinophils based on the change in asthma control.

How does this study impact current management guidelines? This study encourages the clinician to monitor eosinophilic inflammation to reduce it as much as possible, and also highlights that a part of patients with asthma may tolerate an increase in sputum eosinophils.

BACKGROUND: Longitudinal trials have suggested that asthma control may be influenced by fluctuations in eosinophilic inflammation. This association has however never been confirmed in daily practice.

OBJECTIVE: To investigate the relationship between asthma control and sputum eosinophils in clinical practice.

METHODS: A retrospective longitudinal study was conducted on 187 patients with asthma with at least 2 successful sputum inductions at our Asthma Clinic. Linear mixed models were used to assess the relationship between asthma control and individual changes in sputum eosinophils. Receiver-operating characteristic curves were constructed to define minimal important differences (MIDs) of sputum eosinophils associated with a change of at least 0.5 in Asthma Control Questionnaire (ACQ) score. Then, a validation cohort of 79 patients with asthma was recruited to reassess this relationship and the accuracy of the MID values.

RESULTS: A multivariate analysis showed that asthma control was independently associated with individual fluctuations in sputum eosinophil count ($P < .001$). In patients with intermittent/persistently eosinophilic asthma, we calculated a minimal important decrease of 4.3% in the percentage of sputum eosinophils (area under the curve [AUC], 0.69; $P < .001$) or 3.4-fold (AUC, 0.65; $P = .003$) for a significant improvement in asthma control and a minimal important increase of 3.5% (AUC, 0.67; $P = .004$) or 1.8-fold (AUC, 0.63; $P = .02$) for a significant worsening in asthma control. The association between asthma control and sputum eosinophils and the accuracy of the MIDs of sputum eosinophils were confirmed in the validation cohort.

CONCLUSIONS: At the individual level, asthma control was associated with fluctuations in sputum eosinophil count over time. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Asthma control; Sputum eosinophils; Longitudinal study; Daily practice*

Asthma is defined by the Global Initiative for Asthma as a chronic inflammatory disorder of the airways, involving multiple inflammatory cells including eosinophils.[1]

It is now well established that a relationship exists between sputum eosinophilic inflammation and the rate of asthma exacerbations.[2] Previous prospective studies have indeed consistently shown that treatment strategies aiming at reducing the percentage of sputum eosinophils were more effective in decreasing the number of exacerbations than treatment based on usual care in patients with moderate to severe asthma.[3]

In contrast to what has been shown for exacerbations, the association between sputum eosinophilic inflammation and asthma control has been less firmly established. Asthma control is

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Abbreviations used
ACQ- Asthma Control Questionnaire
ACQ-6- Asthma Control Questionnaire 6 items (ACQ score excluding FEV_1)
AUC- Area under the curve
FENO- fractional exhaled nitric oxide
ROC- Receiver-operating characteristic

however another important goal of asthma management,[1] and its relationship with eosinophilic inflammation is important to understand. Several cross-sectional studies showed that patients with a poorly controlled asthma or a more severe disease had higher levels of sputum eosinophils.[2,4-7] However, this association has not been consistently found in all transversal studies.[2,8,9] In a recent study looking at a large series of patients with asthma recruited in daily practice, the relationship between eosinophilic inflammation and asthma control has been further highlighted. It appeared that the combination of systemic and airway eosinophilic inflammation makes asthma particularly difficult to control.[10] There is also indirect evidence for this relationship in longitudinal studies.[2] Initiating a treatment with inhaled corticosteroids (ICSs) resulted in an improvement in asthma control together with a decrease in sputum eosinophilic inflammation,[11-13] whereas a degradation in asthma control was concomitant with an increase in airway eosinophilic inflammation in case of withdrawal or tapering of ICSs.[14,15] Nevertheless, in a recent study, Cowan et al[16] have not found any relationship between the extent of decrease in sputum eosinophils and the extent of clinical response (including asthma control) after a 28-day treatment with a high dose of ICSs. The association between asthma control and changes in fractional exhaled nitric oxide (FENO) over time in daily practice was evidenced in a previous study,[17] but this relationship has never been investigated in real life for sputum eosinophils.

This longitudinal study was carried out to investigate the relationship between asthma control and individual variations in sputum eosinophils over time, in a population of patients with asthma from daily practice who underwent at least 2 sputum inductions in a time frame varying from a few weeks to several years. Second, we sought to define cutoff changes in sputum eosinophils corresponding to individual significant variations in asthma control.

METHODS

Study design, setting, and participants

We conducted a retrospective longitudinal study on patients with asthma of varied severity recruited from the University Asthma Clinic of Liege, Belgium. The reasons to send patients to our Asthma Clinic were at the discretion of the pneumologists of the institution: diagnostic, worsening of asthma, routine follow-up, or follow-up after initiating or changing the treatment.

Patients were included in an initial cohort if they underwent 2 or more visits with a successful sputum analysis between October 1, 2003 (start of our Asthma Clinic), and January 1, 2014. From 301 patients with asthma with at least 2 visits to the Asthma Clinic during this study period, 187 patients were eligible for the study.

To validate the results of the initial cohort and to determine the accuracy in another population of the minimal important difference of sputum eosinophils derived from the initial cohort, we recruited 79 patients for a validation cohort. Patients were included in this validation cohort if they underwent 2 or more visits with a successful sputum analysis, of which at least 1 occurred between January 1, 2014, and April 1, 2016. All selected patients were different from patients of the initial cohort.

For both cohorts, the diagnosis of asthma was based on the presence of typical symptoms (wheezing, breathlessness, chest tightness, cough) and at least 1 of the following: FEV_1 increase of 12% or more and 200 mL after inhalation of 400 μg salbutamol or a provocative concentration of methacholine causing a 20% fall in FEV_1 of less than 16 mg/mL.

This study was conducted with approval from the ethics committee of the University Hospital of Liege (Ref 2014/254).

Variables

All variables used for the analysis were recorded during the routine visits to the Asthma Clinic. Atopy was defined by the presence of at least 1 positive specific IgE (>0.35 kU/L; Phadia; Groot-Bijgaarden, Belgium) to 1 or more common aeroallergen (cat, dog, grass pollen, tree pollen, house dust mite, and a mixture of moulds). Sputum induction and processing were performed as previously described,[18] using the whole expectorate technique, and detailed procedures are described in the Methods section in this article's Online Repository at www.jaci-inpractice.org. The success rate of sputum induction and analysis in our Asthma Clinic was 80% (599 of 746 patients with asthma). The eosinophilic phenotype was defined as a sputum eosinophil count of 3% or more, and the noneosinophilic phenotype as a count of less than 3%.[19] FENO measurements were performed at a flow rate of 50 mL/s (NIOX, Aerocrine, Sweden). Blood analysis was performed by our routine laboratory. Asthma Quality of Life Questionnaire[20] and Juniper Asthma Control Questionnaire (ACQ)[21] were used to estimate quality of life and asthma control in patients with asthma.

Statistical methods

Continuous variables were presented as mean and SD when normally distributed or as median and interquartile range when not normally distributed. Categorical variables were presented as frequencies and percentages.

Paired tests were performed to compare the first and last visits of patients. For continuous variables, the paired *t* test was used when the differences were normally distributed and the Wilcoxon matched-pairs signed-rank test was used when the differences were not normally distributed. The McNemar test was used for binary variables, and the symmetry test was used for categorical variables when there were more than 2 categories.

Linear mixed models were used with the score of Asthma Control Questionnaire 6 items (ACQ score excluding FEV_1) (ACQ-6) as the dependent variable. These models were used on the database including all visits of each patient (from 2 to 9 visits per patient in the initial cohort, and from 2 to 4 visits per patient in the validation cohort). In these models, we used a random intercept for the patient to allow all subjects to have their own intercept, and a random slope for time. For each time-varying independent variable (sputum eosinophils, FENO, blood eosinophils, FEV_1, FEV_1/forced vital capacity, ICS, and oral corticosteroid dose), we calculated 2 derived variables to enable us to dissociate the "within-subject" effects from the "between-subject" effects. Taking the example of the percentage of sputum eosinophils, the "between-subject" variable corresponds to the mean value of sputum eosinophils (%) for each subject (1 mean value per patient, assigned to each visit of this patient). The "within-subject" variable corresponds, for each patient's visit, to the deviation between the measured percentage of sputum eosinophils at