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Letters

Does peripheral blood eosinophil count predict lung function improvement in adult asthmatic subjects?

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Previous studies have investigated the contribution of the eosinophilic phenotype, as defined by the peripheral blood eosinophil count, in predicting asthma outcomes. There is evidence that the eosinophilic phenotype predicts uncontrolled symptoms and asthma exacerbations^{1, 2}. We are aware of no prospective study evaluating whether the eosinophilic phenotype is a useful biomarker for predicting lung function trends in asthmatic subjects who have used maintenance therapy. This is an important issue, because predicting loss of lung function is a meaningful goal of asthma monitoring, as lung function decline leads to irreversible airway obstruction and worse clinical outcomes^{3, 4}. In this study, our aim was to evaluate prospectively whether the eosinophilic phenotype predicts greater lung function improvement and resolution of airway obstruction in asthmatic subjects using maintenance therapy, as compared to the non-eosinophilic phenotype.

We screened consecutive asthmatic subjects who attended an appointment at eight outpatient healthcare settings in Jundiaí City, Brazil, from August 2017 to August 2019. The IRB-FMJ approved the study (2.198.023). Subjects signed informed consent. The inclusion criteria were a doctor's asthma diagnosis, age $\geq$ 18 years old and regular follow-up with a physician. Exclusion criteria were previous smoking history above nine pack-years, current smoking and pregnancy.

The tools for asthma diagnosis were clinical examination and spirometry. Two physicians validated the diagnosis. Spirometry must have shown an improvement

greater than 12% of FEV₁ after bronchodilator administration in any single test performed during the preceding year or between two separated tests.

This is a one-year cohort study. The volunteers attended five quarterly study visits, named V₁ to V₅. At each study visit, subjects underwent evaluation with a chest physician for assessing asthma control and titrating maintenance therapy. On V₁ and V₅, the participants underwent a spirometry test, answered the Asthma Control Questionnaire to assess the severity of symptoms and the Morisky questionnaire to assess the adherence to maintenance therapy. At the V₁, a peripheral blood sample was collected for eosinophil count.

The definition of the eosinophilic phenotype was peripheral blood eosinophil count above 300 cells/mm³. We defined lung function improvement if FEV₁ or FVC had increased more than 50 ml in V₅ as compared to V₁³. Resolution of airway obstruction was defined by the absence of airway obstruction at the V₅ in subjects who presented airway obstruction at the V₁.

We performed binary logistic regression analyses to evaluate whether the eosinophilic phenotype of asthma predicts lung function improvement and resolution of airway obstruction during the follow-up (SPSS 25). Regression analyses were adjusted for age and dose of inhaled corticosteroids (ICS) at enrollment because aging and ICS might modify the number of peripheral blood eosinophils and the spirometry test values^{5, 6}. We adjusted the analyses for the spirometry test values at baseline, as subjects with better baseline lung function

would have less room for lung function improvement. The analyses were adjusted for gender and body mass index because these variables were associated with the study groups at the V_1 .

The research team enrolled 352 asthmatic subjects, 114 eosinophilic and 238 non-eosinophilic. At baseline, eosinophilic subjects were more frequently male (38% & 25%), had lower age (median 48 & 56, in years) and better spirometry test values than non-eosinophilic subjects. Considering the overall sample, the daily dose of ICS and the proportion of subjects reporting controlled asthma symptoms increased from V_1 to V_5 . The FVC or FEV_1 values have increased more than 50 ml in around 30% of the subjects while at least one of these measurements have increased in 172 subjects. During the follow-up, the variation of the ICS dose was similar between eosinophilic (mean; + 119 mcg/day) and non-eosinophilic (mean; + 110 mcg/day) subjects (p 0.77). The median FEV_1 and FVC gain exceeded 200 ml among the 172 subjects who had improved at least one of these spirometry test parameters. Regression analyses showed that asthmatic subjects with the eosinophilic phenotype had higher odds of improving FEV_1 above 50 ml and were more likely to resolve the airway obstruction during the follow-up as compared to the non-eosinophilic subjects (Table 1).

In this study, we demonstrated that subjects with eosinophilic asthma receiving maintenance therapy were more likely to improve lung function and resolve airway obstruction than non-eosinophilic asthmatic subjects. We do not foresee bias related to unbalanced optimization of asthma maintenance therapy during the

follow-up because both study groups have increased the daily dose of ICS in the same amount. Additionally, we adjusted the analyses for all the potential confounders we have recognized. The practical implication of these results is that we identified an accessible biomarker for predicting lung function trends and resolution of airway obstruction in asthmatic subjects receiving maintenance therapy.

We surmised that the eosinophilic phenotype predicted significant lung function improvement, because the FEV₁ and FVC gain exceeded 200 ml among the subjects who had improved lung function during the follow-up and the odds of resolving post-bronchodilator airway obstruction was 27% higher in the group with the eosinophilic phenotype as compared to the non-eosinophilic subjects.

The cross-sectional analyses of baseline data showed that the age at enrollment was lower in the group with high peripheral blood eosinophil count. This association was driven by the physiologic decline of the peripheral blood eosinophil count after eighteen years of age ⁷. It explains the occurrence of better baseline spirometry test values in our group of eosinophilic asthma, as young subjects have better lung function ⁸. Thus, the baseline characteristics of the study groups match with the features in the general population, which supports that the recruitment strategy was effective in obtaining a representative sample. In order to avoid bias related to these differences, the regression analyses were adjusted for these confounders.

In conclusion, our study demonstrated that asthmatic subjects with the eosinophilic phenotype have higher odds of improving lung function and resolving airway obstruction as compared to non-eosinophilic asthmatic subjects. Our conclusions apply to subjects taking maintenance therapy. We recommend future studies for assessing the usefulness of this biomarker for titrating asthma maintenance therapy.

Authors contribution:

Eduardo Vieira Ponte (guarantor of the paper) and Juçara Noeli Silva contributed to literature search, data collection, study design, data analysis, manuscript preparation, manuscript review

Alcides Rocha, Ivani Souza and Rodrigo Athanazio contributed to literature search, data analysis, manuscript preparation, manuscript review

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Conflict of interest

All authors declare no conflict of interest

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Table 1. Binary logistic regression analyses to evaluate whether the eosinophilic phenotype of asthma, according to the peripheral blood eosinophil criterion, predicts lung function improvement during the follow up. (n=352)

	Crude OR (95% CI)	Adjusted OR (95% CI)*
> 50 ml pre-bronchodilator FVC improvement during the study period	-	-
Peripheral blood eosinophil count $\leq$ 300 cells per mm ³	-	-
Peripheral blood eosinophil count > 300 cells per mm ³	1.34 (0.83-2.14)	1.39 (0.86-2.23)
> 50 ml post-bronchodilator FVC improvement during the study period	-	-
Peripheral blood eosinophil count $\leq$ 300 cells per mm ³	-	-
Peripheral blood eosinophil count > 300 cells per mm ³	1.51 (0.95-2.41)	1.56 (0.95-2.58)
> 50 ml pre-bronchodilator FEV ₁ improvement during the study period	-	-
Peripheral blood eosinophil count $\leq$ 300 cells per mm ³	-	-
Peripheral blood eosinophil count > 300 cells per mm ³	1.55 (0.97-2.47)	1.68 (1.04-2.72)
> 50 ml post-bronchodilator FEV ₁ improvement during the study period	-	-
Peripheral blood eosinophil count $\leq$ 300 cells per mm ³	-	-
Peripheral blood eosinophil count > 300 cells per mm ³	1.97 (1.23-3.14)	1.80 (1.09-2.97)
Resolution of pre-bronchodilator airway obstruction during the follow-up**	-	-
Peripheral blood eosinophil count $\leq$ 300 cells per mm ³	-	-
Peripheral blood eosinophil count > 300 cells per mm ³	2.53 (1.12-5.69)	2.65 (1.08-6.55)
Resolution of post-bronchodilator airway obstruction during the follow-up**	-	-
Peripheral blood eosinophil count $\leq$ 300 cells per mm ³	-	-
Peripheral blood eosinophil count > 300 cells per mm ³	2.33 (1.11-4.89)	2.99 (1.27-7.02)

*Adjusted for age, gender, baseline BMI, baseline lung function and dose of inhaled corticosteroids during the follow-up

171 **We enrolled in this analysis only subjects with airway obstruction at the V_1
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