



Letters

Exhaled nitric oxide measurements are not influenced by anti-eosinophil therapy in patients with asthma

A retrospective analysis

The heterogeneity of well-defined type 2 (T2) asthma is reflected by the lack of uniform response to T2 blockade despite the recruitment of patients with a strong T2 signal. The fractional exhaled nitric oxide (FeNO) is a biomarker elevated in uncontrolled T2 asthma secondary to interleukin (IL)-13–induced nitric oxide synthase expression in the airway epithelium. Although FeNO is reduced by anti-immunoglobulin E (IgE) and anti-IL-4/13 therapies,^{1–5} it did not change in studies with mepolizumab, suggesting the lack of modulation by anti-eosinophil therapy.⁶

This retrospective, single-center analysis investigated the FeNO trajectories with anti-IL-5 therapies in a real-world cohort. The patients included in the study were patients with adult-onset severe asthma receiving anti-IL-5 agents for at least 3 months. Patients who were nonadherent during the 3 consecutive months of study and those receiving additional oral corticosteroids (OCS) above their baseline dose, if any, at the time of FeNO measurement were excluded. Patients receiving omalizumab with the predominantly adult-onset disease were chosen as controls because of the known relationship between FeNO and omalizumab.^{4,5,7} We adjusted for the differences in baseline characteristics between the 2 groups, such as blood eosinophil count (BEC), maintenance OCS, IgE, and nasal polyps.

Our objective was to determine the effect of anti-eosinophil agents on FeNO. We also sought to determine whether patients with elevated FeNO (≥ 50 parts per billion [ppb]) are more responsive to IL-5 blockade. The end points for treatment efficacy were asthma symptoms (based on a composite of asthma control test scores and physician assessment) and lung function (an increase of forced expiratory volume in 1 second [FEV1] of ≥ 100 mL) at 3 months.

The baseline characteristics were compared using the independent group *t* test for continuous data and χ^2 test for categorical variables. The analysis of covariance was used to adjust for variables that were significantly different between treatment groups at baseline. The Spearman rank correlations were calculated to measure the association between FeNO and spirometry data.

A total of 47 (44.3%) of 106 patients initiated on anti-IL-5 agents during the study period met the inclusion criteria and were included in analysis. A total of 25 patients were initiated on mepolizumab, 9 on reslizumab, and 13 on benralizumab. In addition, 24 patients had a FeNO greater than 50 ppb before treatment initiation, and 18 patients were treated with maintenance OCS, 11 of whom had FeNO greater than 50 ppb. Of note, there were

significant differences between the study patients and controls with respect to age (55.7 ± 14.4 vs 46.8 ± 12.5 , $P = .009$), age at diagnosis (38.7 ± 13.4 vs 28.1 ± 18.3 , $P = .01$), baseline FeNO (61.8 ± 47.1 vs 42.1 ± 48.1 , $P = .007$), BEC (933.4 ± 646.4 vs 236.3 ± 217.5 cells/ μ L, $P < .001$), and nasal polyps (38% vs 13%, $P = .02$). The unadjusted comparison between the baseline and follow-up data were tested using repeated measures analysis of variance, and the analysis of covariance was used to adjust for variables that were significantly different between treatment groups at baseline.

The mean baseline FeNO for patients using anti-IL-5 was 62 ppb (± 47 ppb), increasing to 74 ppb (± 64 ppb) at 3 months ($P = .64$) (Fig 1). This was similar across the following anti-IL-5 agents used: 61 ppb (± 46 ppb) for mepolizumab, 66 ppb (± 73 ppb) for reslizumab, and 62 ppb (± 26 ppb) for benralizumab. The mean FeNO change over 3 months stratified by anti-IL-5 agent used was plus 18 ppb for mepolizumab, unchanged for reslizumab, and plus 10 among benralizumab users. In contrast, FeNO measurements exhibited a consistent decline among all patients receiving omalizumab, from a baseline of 42 (± 48) ppb to 22 (± 18) ppb at 3 months ($P = .003$) (Fig 1).

Patients with a baseline FeNO greater than 50 had a mean increase of 9 ppb, which was not significant compared with the remainder of the cohort ($P = .74$). Similarly, there was no difference in the FeNO changes among the OCS dependent subgroup and all-comers.

Patients in the anti-IL-5 group had decreased symptoms and improved FEV1 at 3 months. The baseline FEV1 improved from 1.89 L (± 0.72 L) to 2.14 L (± 0.76 L) at 3 months ($P = .06$). Similar improvements in FEV1 were observed among controls, with an increase from 2.09 L (± 0.70 L) to 2.33 L (± 0.64 L) on follow-up. No correlation was found between treatment efficacy and FeNO levels among all anti-IL-5 agents. In particular, there was no correlation between FeNO and FEV1 in the degree of change between baseline and 3 months in the anti-IL-5 group ($r = 0.08$, $P = .58$), although there was a nonsignificant negative correlation between FeNO and FEV1 among the control patients ($r = -0.30$, $P = .10$).

We described FeNO trends in an overall homogeneous cohort of patients with asthma receiving anti-IL-5 therapies. Although some authors have reported a close correlation of FeNO with sputum eosinophils,⁸ others found this association in only 78% of cases.⁹ Because FeNO and eosinophilia are driven by IL4-IL13 and IL-5, respectively, which are produced by various cells, the correlation is not absolute. Relative productions of IL4-IL13 and IL-5 determine its trajectory. Therefore, FeNO is not a surrogate for sputum eosinophils but rather a parallel marker of T2 inflammation.

In the context of biologics, the evidence suggests that FeNO may also be useful as a surrogate biomarker for the assessment and

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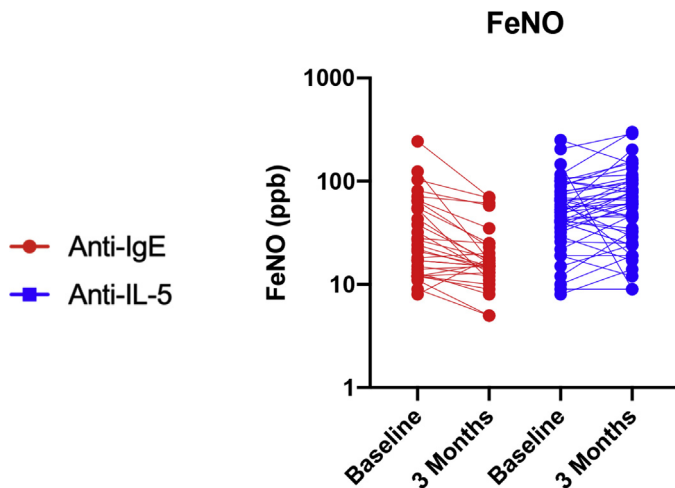


Figure 1. FeNO decreases over 3 months in response to omalizumab but not with anti-IL-5 therapies. FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; ppb, parts per billion.

management of severe asthma and to predict the responsiveness to some biological therapies. However, FeNO greater than 50 ppb was not predictive of decreased asthma exacerbations with mepolizumab.⁶ In contrast, FeNO was a robust predictor of response to dupilumab and progressively declined with treatment. Patients with a FeNO of less than 25 ppb did not exhibit clinical improvement.¹⁰ Similarly, omalizumab-treated patients with a FeNO greater than 19.5 ppb had decreased exacerbations, regardless of BEC.⁴ Omalizumab-treated patients were, thus, chosen for comparison in our study because of this association. We attempted to match patients for all possible treatment-effect modifying factors. However, there were significant differences at baseline that were adjusted for in the analysis.

We did not find significant decreases in FeNO with anti-IL-5 therapies, despite significant improvement in clinical symptoms and FEV1. The marginal increase in FeNO may have been secondary to the weaning of maintenance OCS and a decrease in acute flares requiring steroids rather than a direct effect of anti-IL-5 treatments. However, this was difficult to account for in our study cohort.

The major weaknesses of this study are the limitations associated with the retrospective design and possible confounding by previous and intercurrent oral or parenteral steroids. Our lack of association may also have been because of the small sample size.

In our cohort, FeNO was dissociated from clinical improvement on anti-IL-5 therapies. Although the precise effects of eosinophil depletion cannot be deduced from this limited series, our findings highlight a possible discrepancy between the FeNO trend and treatment response.

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Richard P. Ramonell, MD*
F. Eun-Hyung Lee, MD*
Joshua M. Levy, MD, MPH†
Merin Kuruvilla, MD*

*Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine
Department of Medicine
Emory University School of Medicine
Atlanta, Georgia

†Department of Otolaryngology—Head and Neck Surgery
Emory University School of Medicine
Atlanta, Georgia
merin.kuruvilla@emoryhealthcare.org

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