A retrospective analysis of exhaled nitric oxide measurements in severe asthmatics receiving anti-eosinophil therapy

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Abstract

With the assortment of biologic therapies now available for asthma, it is critical to identify biomarkers of type-2 (T2) inflammation that predict treatment responsiveness. The heterogeneity of even "well-defined" T2-asthma is reflected by the absence of uniform response to T2 blockade despite recruitment of subjects with a strong T2 signal (1). Fractional exhaled nitric oxide (FeNO) is one biomarker that has been used to endotype patients, and identify those with T2-high asthma. In a retrospective, single center observation study, we followed 77 patients with severe asthma who were treated with anti-IL-5 therapies (mepolizumab, reslizumab, and benralizumab) and anti-IgE therapies (omalizumab) as controls. Measurements of FeNO before and after anti-IL-5 therapies were evaluated in a real-world cohort. While FeNO was reduced by anti-IgE, it did not change in the patients treated with anti-IL-5 therapies. Together, these data show that FENO may not be a reliable biomarker of T2-high asthma response to anti-IL-5 therapies although simultaneous reduction of oral corticosteroids may have confounded these results.

Introduction

- Fractional exhaled nitric oxide (FeNO) is one biomarker that has been used to endotype patients, and identify those with T2-high asthma
- FeNO is elevated in uncontrolled asthma through IL-13-induced nitric oxide synthase expression in the airway epithelium
- Elevated values are considered a surrogate of T2 inflammation
- While FeNO is reduced by anti-IgE and anti-IL-4/13 therapies (2-6), it did not change in studies with mepolizumab, suggesting absence of modulation by anti-eosinophil therapy (7)

Methods

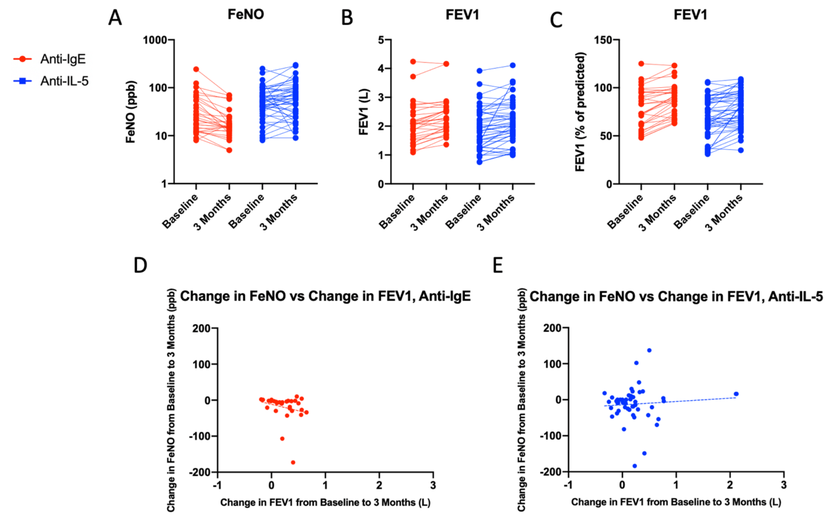
- We performed a retrospective, single center, observational study investigating FeNO trajectories with anti-IL-5 therapies in a real-world cohort. Patients included in the study were adult-onset severe asthmatics receiving anti-IL-5 agents between 01/01/2016 and 09/30/2018 for at least three months. Patients receiving additional oral corticosteroids (OCS) at time of FeNO measurement were excluded. Subjects receiving omalizumab with were chosen as the control group due to the known relationship between FeNO and omalizumab responsiveness (5, 6, 8). We adjusted for differences in baseline characteristics between the two groups, such as absolute eosinophil count (AEC), maintenance OCS, IgE, and nasal polyps (NPs)
- Baseline characteristics were compared using independent group t-test for continuous data and Chi-squared test for categorical variables. Analysis of covariance was used for the adjusted analysis to compare variables that were significantly different between treatment groups at baseline. Spearman rank correlations were calculated to measure association between FeNO and spirometry data. The study was approved by the Emory University Institutional Review Board (IRB00110717), and supported by NIH T32HL116271-07

Results

Table 1: Baseline demographic and clinical characteristics of patients. Unless otherwise specified, all numbers are presented as mean±SD. Baseline characteristics were compared using independent group t-test for continuous data and Chi-squared test for categorical variables. Significant differences were noted between study patients and controls with respect to age (p=0.0078), age at diagnosis (p=0.0113), baseline FeNO (p=0.0065), AEC (p<0.0001), and NPs (p=0.0180).

Characteristic	Anti-IgE (n = 30)	Anti-IL-5 (n = 47)
Age – yr	46.83±12.51	55.70±14.44
Sex – no. (%)		
Male	7 (23.33)	16 (34.04)
Female	23 (76.67)	31 (65.96)
Age at asthma diagnosis – yr	28.17±18.31	38.77±13.47
Time since asthma diagnosis – yr	18.67±15.50	16.94±11.18
Baseline FeNO – ppb	42.17±48.15	61.87±47.10
Baseline FEV1 – L	2.09±0.70	1.89±0.72
Baseline FEV1 – % of predicted	78.90±20.63	69.00±19.61
Baseline serum absolute eosinophil count – cells/μL	236.33±217.56	933.40±646.40
Baseline serum IgE level – IU/mL	394.88±458.57	392.09±571.04
Baseline OCS dependence – no. (%)	3 (10.00)	18 (38.30)
Nasal polyposis – no. (%)	4 (13.33)	18 (38.30)
Diagnosis of aspirin-exacerbated respiratory disease – no. (%)	0 (0)	14 (29.79)
Biologic – no. (%)		
Omalizumab	30 (100)	0 (0)
Mepolizumab	0 (0)	25 (53.19)
Reslizumab	0 (0)	9 (19.15)
Benralizumab	0 (0)	13 (27.66)
Clinical response to biologic therapy – no. (%)	28 (93.33)	41 (87.23)

Figure 1: FeNO decreases over three months in response to omalizumab but not anti-IL-5 therapies (1A). However, FEV1 increased between baseline and 3 months in both the anti-IgE and anti-IL-5 groups (1B, C). There was no correlation between change in FeNO and change in FEV1 between baseline and three months in either the anti-IgE (1D, r=-0.30) or the anti-IL-5 group (1E, r=0.08).



Results

- Mean baseline FeNO for anti-IL-5 subjects: 62 ± 47 ppb, increasing to 74 ± 64 ppb at 3 months (Figure 1A, *p*=0.6443) - similar across anti-IL-5 agent used
- Mean FeNO change over 3 months stratified by anti-IL-5 agent used: +18 ppb for mepolizumab patients, unchanged for reslizumab, and +10 among benralizumab users
- In contrast, FeNO measurements showed consistent decline among all patients receiving omalizumab, from baseline of 42 ± 48 ppb to 22 ± 18 ppb at three months (Figure 1A, *p*=0.0031)
- Patients with baseline FeNO >50 had a mean increase of 9 ppb, which was not significant compared with the remainder of the cohort (*p*=0.7388)
- Similarly, there was no significant difference in FeNO changes among the OCS dependent subgroup and all-comers
- Patients in the anti-IL-5 group had decreased symptoms, improved FEV1, and improvement between baseline and three months although this result was not statistically significant
- Baseline FEV1 improved from 1.89 L (± 0.72 L) to 2.14 L (± 0.76 L) at three months (Figure 1B, *p*=0.0613) and from 69% of predicted (±19.61%) to 77.45% of predicted (±17.67%) at three months (Figure 1C, *p*=0.1383)
- Similar improvements in FEV1 were observed among controls, with increase from 2.09 L (± 0.70 L) to 2.33 L (± 0.64 L) at follow up (Figures 1B, 1C)
- No correlation was found between treatment efficacy and FeNO levels among all anti-IL-5 agents - no correlation between FeNO and FEV1 in the degree of change between baseline and three months in the anti-IL-5 group (Figure 1E, r=0.08, *p*=0.5753) while there was a non-significant negative correlation between FeNO and FEV1 among controls (Figure 1D, r=-0.30, *p*=0.1016)

Discussion

- We did not find significant decreases in FeNO with anti-IL-5 therapies at three months, despite significant improvement in clinical symptoms and FEV1
- The marginal increase in FeNO may have been secondary to weaning of maintenance OCS and decrease in acute flares requiring steroids rather than a direct effect of anti-IL-5 treatments
- Major weaknesses - limitations associated with retrospective design, and possible confounding by prior and intercurrent oral or parenteral steroids
- Our lack of association may also have been due to small sample size. In our cohort, FeNO was dissociated from clinical improvement on anti-IL-5 therapies
- While precise effects of eosinophil depletion cannot be deduced from this limited series, our findings highlight possible discrepancy between FeNO trend and treatment response
- Larger studies should clarify the implications of eosinophil depletion on FeNO

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