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Early View

Research letter

FeNO is associated with disease burden in the German Asthma Net severe asthma cohort

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FeNO is associated with disease burden in the German Asthma Net severe asthma cohort

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Take home message

In a severe asthma cohort of 1007 patients, high FeNO was associated with chronic rhinosinusitis/polyps, later asthma onset, poor lung function and asthma control, low quality of life, frequent exacerbations, and the need for maintenance OCS. #GANregistry

To the editor,

The fraction of exhaled nitric oxide (FeNO) is a biomarker for type 2 asthma, reflecting the degree of local pulmonary inflammation linked to immune pathways including interleukin (IL) 13 [1]. In clinical practice, FeNO is a reliable marker for inhaled corticosteroid (ICS) responsiveness [2] and the efficacy of biological therapies such as those targeting IL4/IL13 pathways [3,4], as well as the detection of steroid nonadherence or resistance in severe asthma [2]. The prospective Severe Asthma Registry of the German Asthma Net (GAN) enrols patients with severe asthma for in-depth assessment of phenotypes, underlying mechanisms, and therapeutic strategies; GAN has been approved by respective ethics committees, with all included patients having signed informed consent [5]. Prior studies of FeNO either included patients with asthma of any severity [6] or did not involve a comprehensive analysis in a large cohort [7]. We therefore used cross-sectional data from GAN to determine the correlation of FeNO with epidemiologic, laboratory, clinical, lung function, or quality of life parameters and the need for oral corticosteroid (OCS) maintenance therapy in a carefully selected severe asthma cohort to better characterise the severe asthma subtype with high FeNO values.

At the time of data acquisition (October 2019), GAN included 1689 patients with severe asthma as defined by the European Respiratory Society / American Thoracic Society [1], from multiple tertiary referral centres mainly in Germany, but also in Slovenia, Austria, and Croatia [5]. FeNO was measured using any available device, according to the manufacturer's instructions [8]. Patients were included in the analysis if a FeNO measurement was available and excluded only if essential data were missing. Consistent with German and international guidelines [1,9] FeNO values ≥25 ppb were considered elevated; exacerbations were defined as events requiring OCS for ≥3 days, doubling of established OCS dose, or hospitalisation; and thresholds for lung function parameters and exacerbation frequency were established. Controlled asthma was defined by Asthma Control Questionnaire-5 (ACQ5) score <1.5, or Asthma Control Test (ACT) score ≥20, with better asthma quality of life defined by mini Asthma Quality of Life Questionnaire (mAQLQ) score ≥5.4 [1,9]. Hypoxaemia was defined as partial pressure of

oxygen in the blood (pO2) <72 mmHg, and obesity as body mass index (BMI) ≥30 kg/m². Total IgE cut-off was aligned with the German criteria for anti-IgE therapy of 75 U/mL [9]. Information bias was addressed by requiring an online form to be completed on assessment of the patient. Since the registry was initiated as a longitudinal project, data acquisition was not selective or biased towards any hypotheses. The significance level for hypothesis testing was set to 0.05. Due to the exploratory character of the study no adjustment for multiple testing was performed and p-values should be interpreted in a descriptive manner. Analyses were performed in R 4.0.3 program (R Core Team (2021), SPSS version 26 (IBM, Armonk, New York, USA), GraphPad Prism 8.3 (GraphPad, San Diego, USA), and Excel 2013 (Microsoft, Redmond, USA), using two-sample unequal variance t-tests, for FeNO, as well as for patient characteristics as dichotomous variables. A sensitivity analysis was performed, and the predictive value of FeNO on exacerbation rate was determined by calculating the positive predictive value. The influence of patient parameters on FeNO was analysed with regression analysis. The target variable FeNO was transformed through 10's logarithm to adapt to the deviation of the residuals' distribution. For continuous patient parameters, univariate linear regressions and for dichotomous variables t-tests were performed. A multiple covariance analysis was performed for all patient parameters with a p-value < 0.05 and at least 90% non-missing values, FEV_1 in L was excluded because of multicollinearity.

Of the 1007 patients in GAN with available FeNO data, 64% had high FeNO measurements (i.e., ≥25 ppb), 58% were female, and 72% had uncontrolled asthma. The mean age was 50.3 years, BMI 27 kg/m², forced expiratory volume in 1 s (FEV_1) 2.04 L (67% predicted), and median FeNO (interquartile range) 34 (18 – 66) ppb.

Compared to patients with low FeNO, those with FeNO ≥25 ppb had a significantly higher rate of asthma exacerbations, had significantly lower pO_2, FEV_1 (both absolute and % predicted) and FEV_1/FVC ratio, and were significantly older (Table 1a). FeNO ≥25 ppb had a sensitivity of 65% to predict the occurrence of ≥2 exacerbations/year, with a positive predictive value of 61%, and an AUC=0.53 (95%CI: 0.50-0.56). Furthermore, when patients were divided into

categories, significantly higher FeNO levels were associated with: BMI <30 kg/m^2, the presence of chronic rhinosinusitis with nasal polyposis (CRSwNP), age at asthma onset ≥12 years, pO_2 <72 mmHg, lower lung function values (FEV_1/FVC <70% or FVC/IVC <0.93 [the lower limit of normal (LLN) [10]]), poor asthma control (ACQ-5 ≥1.5 or ACT <20), worse asthma quality of life (mAQLQ <5.4), frequent exacerbations (≥2/year), IgE ≥75 U/mL, and maintenance OCS use (Table 1b). These results were corroborated by linear regression analysis (Table 1c), and included in a multiple regression analysis. Here, age, CRSwNP, BMI, as well as FEV_1/FVC, and exacerbations per year were independently significantly associated with FeNO levels (Table 1d). Maintenance OCS therapy showed a borderline significance.

This real-life registry of a representative, carefully characterised, large, severe asthma cohort demonstrated the correlation of FeNO with several epidemiologic factors, lung function, asthma control, and asthma quality of life. This broadens our insight into severe asthma, and strengthens the role of FeNO in identifying patients who are at risk of frequent exacerbations.

Our data support the findings that patients with severe asthma with high FeNO values and CRSwNP may be the ideal candidates for anti-IL-4/IL-13R therapy (dupilumab) therapy, which has been approved in Germany for treatment of severe asthma with type 2 inflammation as well as CRSwNP that is inadequately controlled by nasal corticosteroids and surgery [3,9]. Importantly, obesity, considered a hallmark of a non-type 2 phenotype in other cohorts [11], was associated with lower FeNO values. In addition to altered airway mechanics [12], obesity is known to interfere with nitric oxide generation by inducible nitric oxide synthase through a lower ratio of L-arginine to asymmetric dimethylarginine, which could lead to reduced FeNO but increased oxidative stress [13].

Regarding lung function parameters, our association of high FeNO with hypoxaemia has not been described previously. We also observed high FeNO to be associated with reduced FVC/IVC, marking compressive air trapping through reduced lung elastic recoil and increased peripheral airflow resistance [10]. Chronic local inflammation, as indicated by high FeNO, could

lead to airway remodelling over time, linking these two phenomena. These results warrant further evaluation.

Some results corroborate those of existing studies [14-15], including in smaller [7], or less selected asthma cohorts [6], such as the association with age, asthma control, quality of life, exacerbations, and maintenance OCS use. Whilst this cohort was skewed towards type 2 inflammation, cohorts such as the NOVELTY study included a larger portion of non-type 2 asthma patients, and showed similar age, sex, and BMI values, but lower eosinophil count and FeNO values [16]. The main strengths of our study in this regard were the careful selection of patients with severe asthma, and the large cohort size. Indeed, discrepant results vs previous analyses were mainly due to smaller sample sizes in those studies (suggesting that the findings of our study are more likely to be correct), such as our observations of significant associations of FeNO with FEV_1 % predicted and maintenance OCS use in contrast to Mansur et al. [7], with our findings corroborated by others [6,14], and the associations that we observed between FeNO and age of asthma onset, compared to Dweik et al, who recruited a younger population [6].

In conclusion, this study involved a comprehensive evaluation of the biomarker, FeNO, in a large, well-characterised cohort of patients with severe asthma. In severe asthma, FeNO seems to be a sensitive marker for patients at increased exacerbation risk, with a good positive predictive value. Translating these results into clinical practice, we suggest that FeNO can act as a marker of disease burden, and could be a useful parameter in the identification and management of patients with increased risk of complications associated with severe asthma, and those who may require intensified therapy.

Declarations

Author contributions: All authors have committed substantial contributions to either, the conception and design of the study, acquisition or analysis and interpretation of data. All authors have contributed to the drafting and revising of critical concepts of the article manuscript. All authors have spoken their final approval and are in agreement to be accountable for all aspects of the work.

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Conflict of interest:

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Table 1. **Correlation between fraction of exhaled nitric oxide (FeNO) values and patient parameters and demographics**

Table 1a. Parameters associated with FeNO ≥25 ppb

Parameter	N	FeNO ≥25 ppb	FeNO <25 ppb	FeNO ≥25 ppb vs <25 ppb*	
				p-value	95% CI
Age, years	1005	53 (15)	45 (17)	<0.001	–10.02, –5.86
pO_2, mmHg	443	74 (9)	77 (12)	0.002	1.22, 5.28
FEV_1, % of predicted	981	66 (21)	70 (23)	0.033	0.26, 6.15
FEV_1, L	983	2.0 (0.7)	2.1 (0.9)	0.006	0.04, 0.26
FEV_1/FVC, %	950	64 (14)	68 (16)	<0.001	1.57, 5.59
Exacerbations/year	1007	3.5 (4.5)	2.9 (3.4)	0.019	–1.09, -0.10

Table 1b. FeNO levels in categories of patient demographics and characteristics

Parameter	N	Category	FeNO (ppb)	Comparison of FeNO values between categories*	
				p value	95% CI
BMI	1002	<30 kg/m²	52 (49)	0.001	4.12, 15.67
		≥30 kg/m²	42 (37)		
CRSwNP	1007	CRSwNP	54 (49)	<0.001	–16.75, –5.52
		No CRSwNP	43 (42)		
Age at asthma onset	804	≥12 years	54 (49)	<0.001	–24.16, –12.15
		<12 years	36 (33)		
pO_2	443	≥72 mmHg	40 (36)	0.001	–25.27, –6.28
		<72 mmHg	56 (60)		
FEV_1/FVC	950	<70%	53 (49)	0.001	–16.52, –4.92
		≥70%	44 (42)		
FVC/IVC ratio	51	<0.93	55 (53)	0.041	–51.46, –1.16
		≥0.93	29 (27)		
ACQ-5 score	781	≥1.5	51 (51)	<0.001	–19.60, –7.07
		<1.5	38 (35)		
ACT score	927	<20	51 (49)	0.01	–12.89, –1.75
		≥20	43 (35)		
mAQLQ score	746	<5.4	50 (51)	0.006	–16.89, –2.89
		≥5.4	40 (36)		
Exacerbations/year	1007	≥2	52 (49)	0.008	–13.28, –1.99
		<2	45 (42)		
Total IgE	427	≥75 U/mL	53 (50)	0.048	–17.78, –0.08
		<75 U/mL	44 (40)		
Maintenance OCS	1007	Yes	56 (54)	0.001	–16.84, –4.51
		No	45 (40)		

Table 1c. Linear regression analysis, t-test†

Parameter	Estimate	t-value	p-value
BMI, kg/m²	-0.01	-2.94	0.003
Age, years	0.01	6.95	<0.001
pO_2, mmHg	-0.02	-3.81	<0.001
FEV_1, % of predicted	0.00	-2.05	0.040
FEV_1, L	-0.10	-2.73	0.006
FEV_1/FVC, %	-0.01	-4.03	<0.001
ACQ-5 score	0.06	3.07	0.002
Exacerbations/year	0.02	3.54	<0.001
Blood eosinophils/µL	0.00	5.91	<0.001
BMI ≥30 kg/m²†	-	2.7	0.008
CRSwNP†	-	-4.5	<0.001
Age at asthma onset ≥12 years†	-	-5.7	<0.001
Asthma control, defined by ACQ-5†	-	-2.8	0.005
Maintenance OCS†	-	-3.4	<0.001

Table 1d. Multiple linear regression analysis

Parameter	Estimate	t-value	p-value
Age, years	0.004	5.323	<0.001
BMI, kg/m²	-0.007	-3.292	0.001
CRSwNP	0.087	3.577	<0.001
FEV_1, % of predicted	0.001	1.302	0.193
FEV_1/FVC, %	-0.003	-2.247	0.025
Exacerbations/year	0.009	2.968	0.003
Maintenance OCS	0.049	1.930	0.054

Table 1. Correlation between fraction of exhaled nitric oxide (FeNO) values and patient parameters and demographics. a) Patients with severe asthma were divided into FeNO high (FeNO ≥25 ppb) and FeNO low (FeNO <25 ppb) groups. b) Patients with severe asthma were categorised based on their demographics and characteristics, and FeNO values were determined. c) Univariate regression analyses and t-tests with the target variable log(10) FeNO, for continuous independent patient variables, regression estimate, t-statistic and p-value are reported, for dichotomous independent variables, t-test t-statistic and p-value are provided. d) Multiple linear regression analysis with the target variable log(10) FeNO, 64 patients were excluded due to missing data.

*p values and CIs are for the mean difference between groups or categories from the T-test. Other data are mean (standard deviation). ŧdichotomous independent parameters. 95% CI are 95% Confidence Interval of the Difference. Abbreviations: FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyposis; IVC, inspiratory vital capacity; OCS, oral corticosteroids; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; mAQLQ, mini Asthma Quality of Life Questionnaire; pO_2, partial pressure of oxygen in blood; IgE, immunoglobulin E.