The German Severe Asthma Registry:
FeNO values correlate with medical therapy, quality of life and smoking

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German Asthma Net e.V.

Introduction

FeNO as a marker of airway inflammation lacks large-scale validation for severe asthma. This study aims to elucidate correlations of FeNO with medical therapy, quality of life and smoking in the population of the German Severe Asthma Registry including ≤8 yearly follow-ups of 1340 patients (48 ± 17 yrs., 58 % female, FEV1 2,07 ± 0,82 L, see table 1).

Table 1. Total patients, n=	1340
Doctor appointments per pat.	1,93
Mean age, years	48,44 (±17,26)
Female, %	57,82
Mean BMI, kg/m²	26,86 (± 6,18)

Medical therapy included ICS + LABA + LAMA in 1073, biologics in 1293 and oral steroids (OCS) in 905 of 2582 appointments.

Methods

Retrospective analysis of a severe asthma registry conducted at multiple tertiary referral centres in Central Europe. Patients included from Nov 2010 to Nov 2018 with evaluations including lung function scores, blood and sputum analysis, thorough patient history and medication, quality of life evaluations. Statistical evaluation was conducted with Excel© including student t-test with a cut-off level of p < 0,05.

Conclusions

In this carefully selected severe asthma cohort, increased FeNO levels are associated with OCS-dependency, eligibility for biological-therapy, lower FEV1, higher blood eosinophils, lower ICS-doses and lower asthma control, as well as never smoking status.

Acknowledgement

Bibliography

Fig 2: Zazzali 2015, Hanania 2013, Casale 2019, DiBona 2017, Bhutani 2017
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Who are the **severe asthmatic** patients with **high FeNO values**?

characteristics of all patients with FeNO ≥ 20 ppb	FeNO ≥ 20 b-eos≥150	All pat. w. FeNO<20	FeNO<20 b-eos<150
appointments, n=	767	405	375	171
FeNO, ppb	**60,18**	**62,95**	**12,78**	**12,48**
Eos., cells/µL	419	628	294.44	74
age, years	52	52	45.68	48
female, %	62	58	62	65
late onset > 12y, %	**78**	**77**	**63**	**67**
never smoker, %	46	48	32	27
ACQ mean score	**1,80**	**1,97**	**1,54**	**1,64**
mean FEV1, % of norm	66	64	70	70
mean FEV1/FVC, ratio	0,64	0,64	0,67	0,67
mean exacerbations within 12 months, n=	4,14	4,41	3,56	4,21
CSwNP, %	**56**	**61**	**42**	**47**
therapy: ICS high dose, %	46	48	43	49
therapy with OCS, %	**45**	**42**	**28**	**35**
therapy: all biologicals, %	**54**	**52**	**58**	**61**
OCS and/or biologicals, %	**77**	**74**	**75**	**82**

Table 2. The **typical high FeNO candidate** is female, 52 years old, shows a mean FeNO value of 60 ppb and blood eosinophilia with 0,4 G/L, shows uncontrolled asthma with an ACQ score of 1,80 and limited lung function with 66% of FEV1 capacity norm.
Intriguingly, more than 4 exacerbations per year of any severity are reported and chronic sinusitis or nasal polyposis (CSwNP) are prevalent in more than half of patients. Most had limited or no contact to cigarette smoke.
Patients additionally burdened **with blood eosinophilia** (b-eos) show higher mean FeNO values of 63 ppb, worse quality of life with a mean ACQ score of 1,97 and higher prevalence of sinusitis and polyposis.
In contrast, a **typical low FeNO/low b-eos- candidate** is also female, 48 years old, shows better controlled asthma (mean ACQ 1,64) with a better FEV1 mean of 70% of norm. As expected, less exacerbations (3,56 vs. 4,14 per year), cases of sinusitis and polyposis are recorded. While OCS use is less prevalent, biological therapy is highly (61%) used in this group of patients.

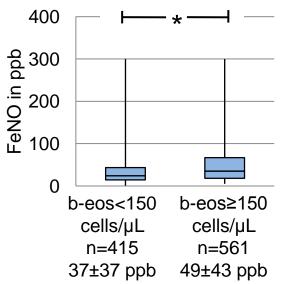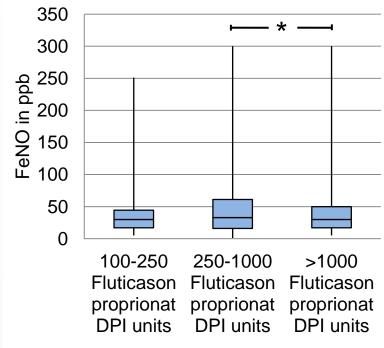## **Blood eosinophilia** is associated with increased FeNO

Figure 6. Blood eosinophilia (defined as ≥ 150 eosinophils /µl blood) showed a significant association with high FeNO values (**p<0,0001**), and a much higher variation of FeNO values, its 3rd quartile reaching 67 ppb FeNO.

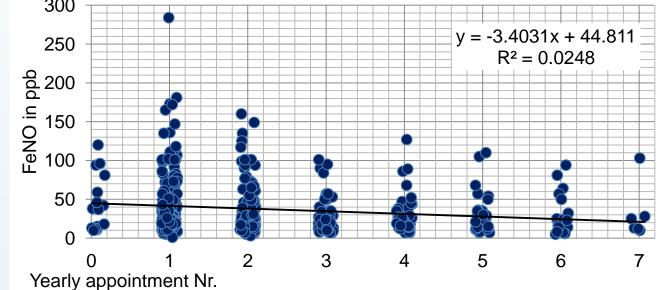## FeNO in inhalative therapy: **low vs. high ICS dose**

low ICS dose: n = **126**   40 ± 39 ppb
moderate ICS dose: n = **713**   47 ± 44 ppb
high ICS dose: n = **287**   41 ± 39 ppb

Figure 1. Inhaled corticosteroid (ICS) dose: FeNO values were significantly higher in patients with moderate ICS dose (equivalent of 250-1000 FP DPI units) compared with patients with high-dose ICS (equiv. of >1000 FP DPI units) therapy regimen (**p=0,03**). ICS doses were applied to groups regardless of concomitant therapy (OCS, biologicals, inhalers).

FeNO decreases with **omalizumab** therapy **duration**

$y = -3.4031x + 44.811$
$R^2 = 0.0248$

At start, n=181: **43 ± 40 ppb**
At 3rd appointment, n=47: **29 ± 23 ppb**

Figure 2. From start of Omalizumab treatment at 3rd, 4th or even 7th year appointment, a sustained reduction in FeNO was shown (**p=0,001**). Likewise, a reduction in **ACQ** score could be achieved (from therapy start (ACQ 1,60±1,09, n=291) to 3rd appointment (ACQ 1,17±0,97, n=69; **p=0,003**). Patient attrition rate (yearly 20%) was comparable to published long term trials (yearly 13-25%).

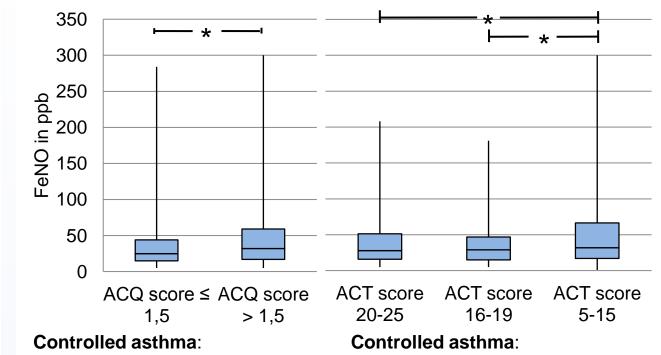## **OCS**-dependence is associated with increased FeNO

Current OCS: n= 448:   52±49ppb
No OCS: n= 694:   40±37ppb

Figure 3. Patients depending on OCS had significantly higher baseline FeNO values than patients without OCS (**p<0,0001**), regardless of inhalative therapy.

Any smoking history reduces FeNO measurements

1 **Non-smoker:**   n=470   50 ± 46 ppb
2 **Passive smoker:** n=1021   43 ± 42 ppb
3 **Ex-smoker:**   n=442   41 ± 40 ppb
4 **Current smoker:** n=30   24 ± 22 ppb

Figure 7. In currently smoking patients, significantly lower FeNO values were shown than in ex-smokers (**p=0,0004**). Non-smokers had the highest FeNO (**p<0,0001**).

Smoking habits and **uncontrolled** asthma:	ACQ > 1,5 ∩ FeNO < 20 ppb	**overall** collective
appointments, n=	146	2582
Current smoker, %	5	2
Ex-smoker, %	53	38
Passive smoker, %	18	19
Non-smoker, %	23	40

Table 4. In accordance with published papers, smoking was a strong **confounder** in regards to patients who had **poorly controlled asthma** as defined by ACQ, yet still showed **low FeNO** values. Strikingly, patients with any positive smoking history made up 77% of this group, of those, current smoking patients only 5%. As such, a high index of suspicion is required while evaluating this subgroup with low-FeNO and high quality of life burden.

High FeNO is associated with **uncontrolled asthma**

Controlled asthma:
ACQ≤1,5, n=**429**:   35 ± 30 ppb

Uncontrolled asthma:
ACQ>1,5: n=**470**:   49 ± 50 ppb

Controlled asthma:
ACT 20-25, n=**376**: 38,61 ± 30,86 ppb
Medium controlled asthma:
ACT 16-19, n=**194**: 38,06 ± 32,61 ppb
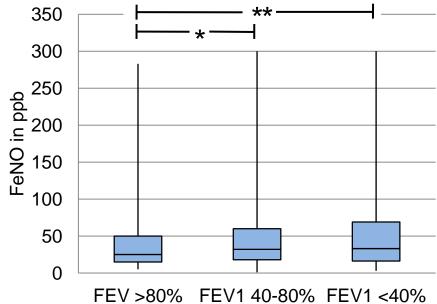**Uncontrolled asthma:**
ACT 5-15,   n=**475**: 50,16 ± 49,87 ppb

Figure 4. As expected, patients reaching asthma control (defined as ACQ ≤ 1,5 and ACT ≥ 20) showed significantly lower FeNO values than uncontrolled patients (**p < 0,0001**).

Table 3. In the group of controlled asthma, 67% of patients received OCS and/or biological therapy, predominantly biologicals, showing a mean FeNO value of 16 ppb. Similarly, in the group of uncontrolled asthma, 66% used OCS + biological therapy. However, an increased use of OCS was noted. Both patients on and off OCS/biolog. therapy had a mean FeNO value of 49 ppb.

Table 3, Asthma control and therapy:	Controlled, n=801 appt.	Uncontrolled n=995 appt.
OCS + biologicals, %	67	66
FeNO, +/- OCS/biol.	16 / 38 ppb	49 / 49 ppb
biologicals, % of total	56	39
OCS, % of total	25	43

Lung function value **FEV1** is inversely associated with FeNO

FEV1>80%: n=349: 39 ± 37 ppb
FEV1=40-80%: n= 673: 46 ± 42 ppb
FEV1<40%: n=118: 56 ± 60 ppb

Figure 5. Patientis with good lung function results (FEV1 > 80% of norm) had significantly lower FeNO values than both patients with medium (**p = 0,005**) and poor results (**p = 0,004**). Patients with poor FEV1 (< 40%) showed the highest FeNO values, with an average of 56 ppb.