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LETTER

German asthma net: Nasal polyposis in patients in the severe asthma registry

To the editor,

Severe asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) are frequently comorbid diseases caused by type 2 inflammation of the airway mucosa. However, whether CRSwNP contributes to a greater asthma disease burden is unclear, and real-life studies provide contrasting results.[1–5]

We assessed disease parameters and underlying inflammation in patients with severe asthma and CRSwNP in the prospective, multicenter German Asthma Net (GAN, https://germanasthmanet.de/en/centers/).[6,7] CRSwNP, sinonasal surgery, treatment, comorbidities, and asthma forms were evaluated based on medical reports and patient history. Targeted treatments were prescribed for severe asthma according to recent German guidelines, with anti-immunoglobulin E (IgE) prescribed for severe allergic asthma with ≥1 perennial aeroallergen and total IgE of 30–1500 U/mL, anti-interleukin (IL)-5-(R) for severe eosinophilic asthma, and anti-IL-4-R for severe asthma with a fraction of exhaled nitric oxide (FeNO) ≥25 ppb or blood eosinophils ≥150/μL.[8] Current treatment with a targeted treatment with ≥1 dose received defined patients under targeted treatment. Continuous parametric variables were assessed by univariate *t*-tests, nonparametric variables by Mann–Whitney *U* Tests, and Chi-Square tests for binary variables, as an exploratory study without adjustments for multiple testing (Data S1).

Patients with severe asthma and CRSwNP (35% of $n=1746$; Table 1, Figure S1) showed significantly higher levels of exhaled nitric oxide (FeNO) and blood eosinophil counts, indicating a more pronounced underlying type 2 inflammation, yet an inverse association with sensitization to perennial and seasonal allergens ($p<.01$). Patients with CRSwNP received significantly more targeted therapy than patients without CRSwNP, with the exception of anti-immunoglobulin E therapy due to the lower prevalence of allergic asthma forms ($p<.0001$, Figure S2). Mean yearly exacerbations, rates of frequent exacerbations (≥2/year), and use of systemic corticosteroids were high regardless of CRSwNP (Figure 1; Table S1). Even though rates of asthma control and health-related quality of life in patients with CRSwNP were significantly higher, the score differences were not clinically relevant (Table 2; Data S1).

The effect of CRSwNP on the burden of disease was clarified when assessing only patients without targeted treatments ($n=963$). Here, patients with CRSwNP experienced pronounced type 2 inflammation, significantly more often any exacerbations, frequent exacerbations, and poor quality of life than patients without CRSwNP, whereas there were no more statistically significant differences between asthma control rates in these two groups (Table 3).

Differences in lung function values between patients with and without CRSwNP irrespective of targeted treatments, were statistically significant, but not clinically relevant (Figure S3).

Type 2 inflammation markers were particularly high in patients with CRSwNP irrespective of Aspirin-exacerbated respiratory disease (Table S2, Figure S4).

The association of coexisting severe asthma and CRSwNP with higher type 2 biomarkers was expected and corroborated by other studies;[2,5] similar to the inverse associations with allergic sensitization, which have been less elucidated in-depth outside of cluster analyses.[1,4,5,9] Surprisingly, we found no association of CRSwNP with high disease burden in the total cohort, in contrast to previous Italian, UK, and French real-life registry studies,[1,2,5] which however partially corroborated our results regarding OCS therapy,[4] exacerbation rates,[3] lung function values,[5] and asthma control.[2,5] Contrasting results are potentially a consequence of the inclusion

Abbreviations: ACQ, asthma control questionnaire; ACT, asthma control test; CRSwNP, chronic sinusitis with nasal polyps; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GAN, German asthma net; IgE, Immunoglobulin E; mAQLQ, mini asthma quality of life questionnaire; OCS, oral corticosteroids.

TABLE 1 Percentages of patients with and without CRSwNP differ in relevant asthma parameters.

Parameter, % of total (*n*)	CRSwNP, % (*n* = 617)	No CRSwNP, % (*n* = 1129)	*p*-value (Chi-Square)
Surgical treatment of CRSwNP	77.3% (477)	n/a	n/a
Chronic sinusitis	n/a	29.5% (333)	n/a
FeNO ≥25 ppb	73.9% (241)	58.9% (334)	<.0001
Seasonal sensitisation (Specific IgE)	16.2% (100)	21.8% (246)	.005
Perennial sensitisation (Specific IgE)	19.0% (117)	25.8% (291)	.001
Predominantly allergic asthma form	39.7% (213)	47.1% (413)	.004
Non-allergic asthma form	35.4% (190)	27.5% (241)	
Any targeted therapy	51.1% (315)	43.2% (488)	<.0001[a]
anti-IL-5/IL-5 (R)	37.9% (234)	23.7% (268)	<.0001
Anti-IL-4/13	5.0% (31)	3.3% (37)	.07
Anti-IgE	8.1% (50)	16.2% (183)	<.0001
Severe exacerbations	53.7% (231)	54.9% (424)	.7
Near-lethal exacerbations	7.5% (32)	7.6% (58)	.9
Beclomethasone equivalent ≥1000 μg/day	53.2% (328)	48.2% (544)	.047
Beclomethasone equivalent ≥2000 μg/day	18.0% (111)	21.7% (245)	.07
LAMA	68.9% (395)	73.8% (747)	.038
Any corticosteroid adverse effects	53.6% (331)	48.0% (540)	.023
ACQ, uncontrolled asthma	69.9% (364)	74.0% (659)	.1
ACT, uncontrolled asthma	67.3% (382)	74.6% (761)	.002
mAQLQ, poor quality of life	79.2% (393)	81.2% (698)	.4
Eosinophilic granulomatosis with polyangiitis	5.2% (32)	1.9% (22)	.0002
Hypereosinophilic syndrome	4.2% (26)	1.9% (21)	.004
Eosinophilic pneumonia	2.4% (15)	0.5% (6)	.0005
NSAID-exacerbated respiratory disease	27.6% (170)	16.3% (184)	<.0001
Acetylsalicylic acid deactivation	2.9% (18)	0.7% (8)	.0003
Current age ≥ 18 years	97.2% (600)	92.5% (1043)	<.0001
Female	53.8% (332)	58.4% (659)	.07
Obesity	26.5% (162)	29.2% (329)	.2
Family history of asthma	74.7% (221)	73.0% (414)	.6
Comorbid COPD	6.6% (41)	9.2% (104)	.063

Note: Patients were separated into subgroups by the presence of nasal polyps, and several clinically relevant parameters in the different groups were assessed. Data are presented as % of the group total (number of patients).

[a]Chi-square test with 5 groups (no therapy, OCS, anti-IL-4/13, anti-IL-5/IL-5(R), anti-IgE).

of different type 2 inflammation levels and severities in studies that include many non-severe asthma patients, or could stem from exacerbations, poor asthma control, additionally to CRSwNP, being characteristic features of heightened underlying type 2 inflammation.[1,2]

The data on CRSwNP was obtained from medical records and patient history, which did not include severity aside from surgery requirement, and conferred a possibly heightened stated rate of CRSwNP.

In this study of the large, well-characterized cohort with severe asthma of the GAN, the presence of CRSwNP marked heightened underlying type 2 inflammation, with increased FeNO and blood eosinophil counts. This study assessed patients with definitionally severe disease, frequent exacerbations, high systemic corticosteroid dependency, and poor asthma control, with the use of targeted therapy in more than 50%. Here, irrespective of CRSwNP, corticosteroid maintenance therapy, and exacerbation rates were similar, and disease control, quality of life, and lung function values were clinically comparable. However, regarding only patients without targeted therapy, CRSwNP was associated with a higher rate of frequent exacerbations and poor quality of life. Relevantly, CRSwNP was highly associated with type-2 inflammatory disease irrespective of current biologic use.

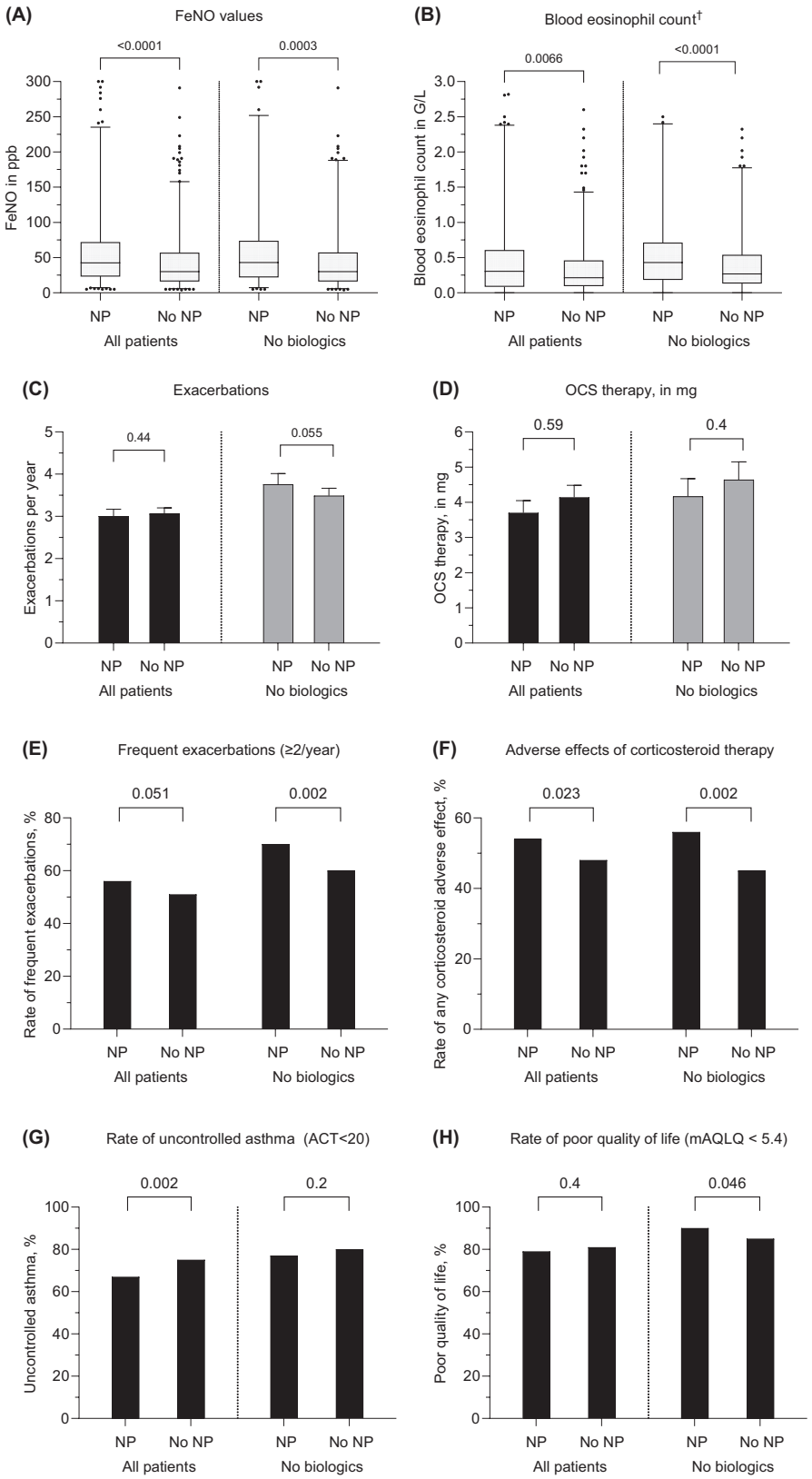

FIGURE 1 Type 2 inflammation markers are significantly higher in patients with CRSwNP. Patients with CRSwNP exhibited higher FeNO values and higher blood eosinophil counts than patients without CRSwNP. This effect persisted in only patients without biologic therapy. Analyses of patients without biologic therapy unmask the higher burden of disease in patients with severe asthma and CRSwNP. ACT, Asthma Control Test. mAQLQ, mini Asthma Quality of Life Questionnaire. FeNO, Fraction of exhaled nitric oxide. NP, nasal polyps. OCS, oral corticosteroids. †: Graph was truncated at 3 G/L for improved visibility.

Parameter, mean (*SD*):	CRSwNP (*n* = 617)	No CRSwNP (*n* = 1129)	*p-value*
FeNO, ppb	57.9 ± 53.7	43.7 ± 41.1	<.0001
Blood eosinophils/µL	472.5 ± 625.7	376.1 ± 690.2	.007
Exacerbation rate	3.0 ± 3.9	3.1 ± 4.3	.4
OCS in mg	3.7 ± 8.5	4.1 ± 11.4	.6
ACQ score (MCID: 0.5 points)	2.5 ± 1.5	2.6 ± 1.5	.15
ACT score (MCID: 3 points)	15.9 ± 5.7	14.9 ± 5.6	.0007
mAQLQ score (MCID: 0.5 points)	4.2 ± 1.4	4.0 ± 1.4	.09
FEV1 in % of predicted (MCID: 5–15%)	71.2 ± 21.2	66.5 ± 23.1	<.0001
FVC, % of predicted (MCID: 5–15%)	83.9 ± 19.6	80.2 ± 19.4	.0006
FEV1/FVC, in %	70.5 ± 13.4	68.6 ± 14.9	.019
RV/TLC, in %	46.7 ± 11.6	48.8 ± 13.4	.013
DLCO, % of predicted	73.3 ± 19.0	69.4 ± 19.4	.018
Asthma onset, years	35.3 ± 17.1	31.8 ± 21.2	.005

TABLE 2 Patients with CRSwNP exhibit significantly higher type 2 inflammation markers.

Note: While lung function and asthma control parameters are higher than in patients without CRSwNP, the difference is not clinically relevant. Further analyzes which did not yield significant differences were omitted (age, BMI, pO2, pCO2, blood neutrophil counts, total IgE).

Selected parameters in patients without targeted treatments, % of total (*n*)	CRSwNP, (*n* = 310)	No CRSwNP, (*n* = 653)	*p*-value (Chi-Square)
Predominantly allergic asthma form	37.2% (109)	45.6% (251)	.07
Non-allergic asthma form	34.1% (100)	29.6% (163)	
Any exacerbations	84.9% (248)	79.3% (486)	.042
Frequent exacerbations	70.2% (205)	59.5% (365)	.002
Beclomethasone equivalent ≥1000 µg/day	53.9% (167)	48.2% (315)	.10
Beclomethasone equivalent ≥2000 µg/day	18.4% (57)	22.1% (144)	.19
LAMA	71.1% (212)	74.4% (445)	.3
Any corticosteroid adverse effects	56.1% (174)	45.2% (294)	.002
ACQ, uncontrolled asthma	79.4% (208)	80.7% (419)	.7
ACT, uncontrolled asthma	76.7% (220)	80.0% (477)	.2
mAQLQ, poor quality of life	89.9% (223)	84.6% (423)	.046
Selected parameters in patients without targeted treatments, mean ± SD:			
FeNO, ppb	59.3 ± 56.6	44.9 ± 43.5	.0003
Blood eosinophils/µL	582.9 ± 678.9	450.5 ± 814.2	<.0001
FEV1 in % of predicted (MCID: 5–15%)	70.0 ± 21.0	64.9 ± 22.8	.002
FVC, % of predicted (MCID: 5–15%)	83.2 ± 19.0	78.5 ± 18.8	.002
RV/TLC, in %	47.0 ± 11.4	49.9 ± 13.3	.012

TABLE 3 In patients without targeted treatments, the impact of CRSwNP on type 2 markers, asthma control, quality of life, and disease burden is unmasked.

Abbreviations: ACQ-5, asthma control questionnaire 5; ACT, asthma control test; COPD, chronic obstructive pulmonary disease; CRSwNP, Chronic sinusitis with nasal polyps; FeNO, Fraction of exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, Immunoglobulin E; IL, interleukin; LAMA, long-acting muscarinic antagonist; mAQLQ, mini Asthma Quality of Life Questionnaire; MCID, Minimal clinically important difference; N-ERD, Aspirin-exacerbated respiratory disease; NSAID, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroids; RV, residual volume; TLC, total lung capacity.

AUTHOR CONTRIBUTIONS

All authors have spoken their final approval and agree to be accountable for all aspects of the work, and have contributed substantially to the conception of the study, analysis and interpretation of data, and revising the article critically for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

CB reports speaker fees from AstraZeneca, IVEPA, OLYMPUS, Sophos Akademie, all outside the submitted work. SS received fees for lectures or consultations from AstraZeneca, all outside the submitted work. KM reports speaker fees from Astrazeneca, GSK, Novartis, Sanofi, all outside the submitted work. DS received fees for lectures or consultations from AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, GSK, Janssen, Novartis, Pfizer. MG reports lecture fees and honoraria for consultancy from ALK, GSK, HAL, Nestle, Novartis, Omron, Sanofi and an institutional grant from Nestle, outside the submitted work. CKR reports speaker fees from Sanofi, outside the submitted work. MJ has nothing to disclose. OS reports speaker fees from Astrazenca, GSK, Sanofi, and Boehringer all outside the submitted work. RE has nothing to disclose. CT has nothing to disclose. EH is funded by the German Ministry of Education and Reserch (BMBF) as consortional partner in CHAMP (01GL1742D) for research in severe asthma in children. RB reports grants to Mainz University and personal fees from Boehringer Ingelheim, GSK, Novartis, and Roche, as well as personal fees from AstraZeneca, Chiesi, Cipla, Sanofi, and Teva, all outside the submitted work. SK reports speaker fees from Astrazenca, GSK, Novartis, Sanofi, all outside the submitted work. MI reports lectures fees from AstraZeneca, Bayer, Berlin-Chemie, Boehringer Ingelheim, Chiesi, CSL-Behring, GSK, Menarini, MSD, Novartis, Roche, Sanofi, Thermofischer and advisory board fees from Alk-Pharma, AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, CSL-Behring, GSK, Novartis, and Sanofi, all outside the submitted work.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.