

Type 2 biomarker expression (FeNO and blood eosinophils) is higher in severe adult-onset than in severe early-onset asthma

To the Editor,

Severe asthma is predominantly associated with a type 2 inflammatory pattern¹; however, it is unclear whether the expression of type 2 biomarkers differs between severe early-onset asthma (SEA) and severe adult-onset asthma (SAA). This issue is of particular importance for the question whether the age of asthma onset can be a helpful clinical information for the selection of targeted treatments (especially biologics) in patients with severe asthma. We analyzed data from patients with severe asthma (not currently treated with biologics) who presented routinely to a specialized severe asthma outpatient clinic in Rostock (Germany). Inclusion criteria and methods are detailed in the Supplement. According to GINA, presence of type 2 inflammation was defined as ≥ 150 eosinophils/ μ l blood and/or FeNO ≥ 20 ppb and/or a history of clinically allergen-driven symptoms.² According to the UK Severe Asthma Registry (UKSAR),¹ a type 2 high phenotype was defined as ≥ 150 eosinophils/ μ l blood and FeNO ≥ 25 ppb, a type 2 low phenotype as < 150 eosinophils/ μ l blood and FeNO < 25 ppb. A type 2 intermediate phenotype was defined by the detection of either ≥ 150 eosinophils/ μ l blood or FeNO ≥ 25 ppb.

A total of 220 adult patients were included: 50 with SEA (symptom onset < 18 years of age) and 170 with SAA (symptom onset ≥ 18 years of age). There were no differences in asthma control, gender distribution, body mass index, history of upper airway diseases, total IgE, inhalation therapies, lung function and diffusion capacity between the groups (Tables S1 and S2). As compared to SEA, SAA was characterized by a higher smoking history, more exacerbations and a higher likelihood of maintenance OCS treatment (Table S1). Patients with SAA had significantly higher FeNO values and blood eosinophils than patients with SEA (Table S2, Figure 1). The correlation between blood eosinophils and FeNO was weak ($r = .18$ in both groups; SEA: $p = .24$, SAA: $p = .02$). A type 2 high phenotype (UKSAR definition¹) was more prevalent in SAA than in SEA (Table S2 and Figure 2). In both groups, $< 10\%$ of the patients had a type 2 low phenotype according to UKSAR¹ (Figure 2), and $< 5\%$ did not have type 2 inflammation according to GINA² (Table S2). In contrast, there was a trend towards lower total serum IgE in SAA as compared

with SEA (Figure 1). In addition, the percentage of patients with clinically reported respiratory allergies to common aeroallergens was much lower in SAA than in SEA (Table S2). Although a history of allergen immunotherapy (AIT) was more prevalent in SEA than in SAA (Table S1), there was no evidence that a history of AIT impacted on type 2 biomarkers: in patients without a history of AIT (38 patients with SEA, 158 patients with SAA), median FeNO values (SEA: 19 ppb, SAA 41 pp) and median blood eosinophils (SEA: 350/ μ l, SAA: 500/ μ l) were nearly identical to the values of the total groups of patients with SEA and SAA. Among patients with SAA, the type 2 high phenotype was more prevalent in patients without clinically reported allergies than in those with clinically reported allergies, despite lower total IgE (Table S3). OCS therapy or a history of nasal polyps impacted on blood eosinophils, but not on FeNO, in SAA (Table S3). In addition, we analyzed SAA subgroups according to the age of asthma onset: 18–40 years (early adulthood) vs. > 40 years at disease onset (later adulthood). Although there was a trend to higher FeNO values and blood eosinophils in patients with a disease onset in later adulthood, there were no significant differences in type 2 biomarkers between these SAA subgroups (Table S3).

This is the first report showing that FeNO values are higher in SAA than in SEA (previous studies investigated FeNO in various patient clusters, but did not compare SEA with SAA³). In addition, although it is generally accepted that intrinsic asthma is associated with higher blood eosinophils than allergic asthma⁴ and that SAA is characterized by stronger tissue and sputum eosinophilia than SEA,^{3,5} our study demonstrates stronger blood eosinophilia in SAA than in SEA. Accordingly, we show that patients with SAA are more likely to meet current criteria of a type 2 high phenotype¹ than patients with SEA. Thus, we hypothesize that SAA is characterized by an intrinsically stronger type 2 inflammation than SEA, reflecting the clinical observation that adult-onset asthma tends to be more severe than early-onset asthma. In addition, the data suggest that the age of asthma onset might serve as a helpful clinical information for the selection of targeted treatments. Indeed, the adult-onset characteristic is already used by clinicians in choosing biologic therapies targeting the Interleukin-5 (IL-5) pathway, because of post hoc data

Abbreviations: FeNO, fractional exhaled nitric oxide; GINA, global initiative for asthma; IgE, immunoglobulin E; OCS, oral corticosteroid; SAA, severe adult-onset asthma; SEA, severe early-onset asthma; UK, United Kingdom; UKSAR, United Kingdom severe asthma registry.

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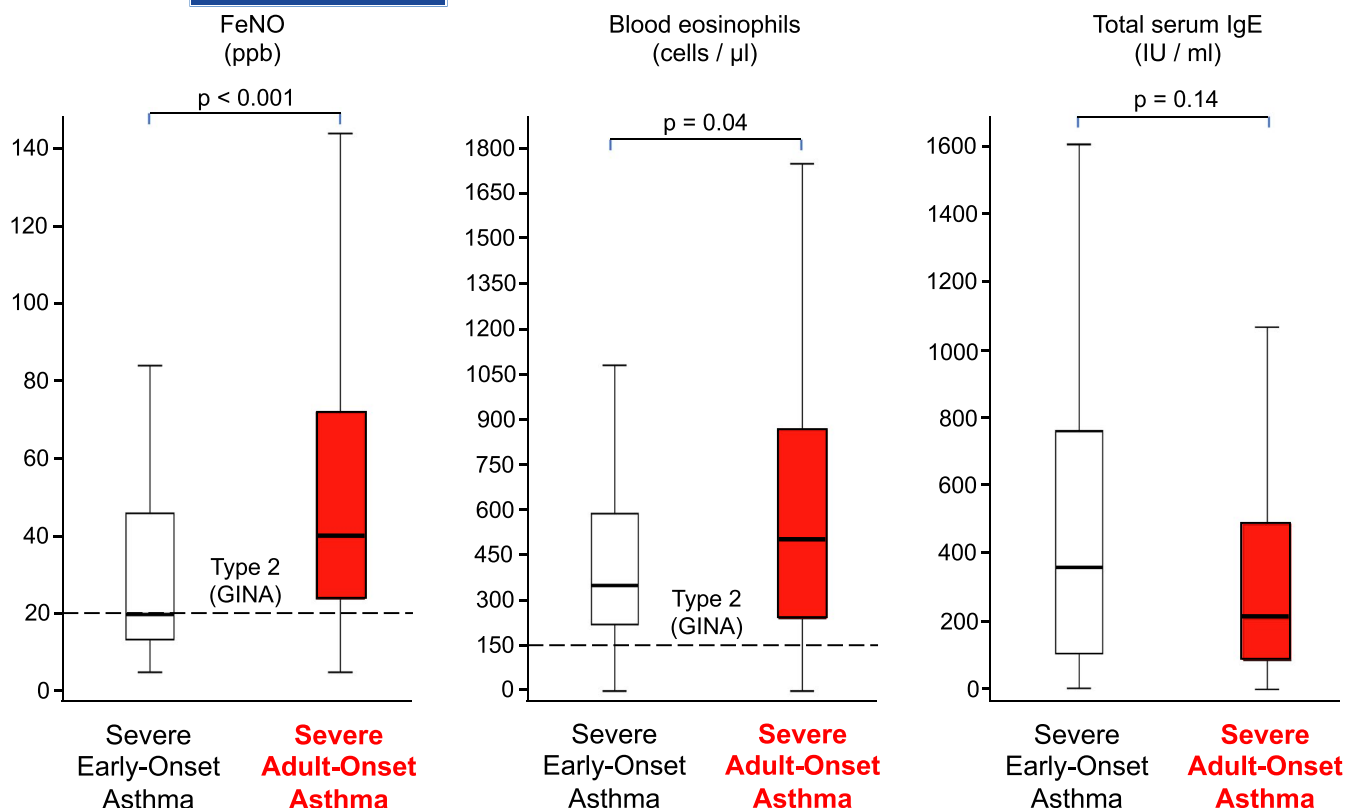


FIGURE 1 Fractional exhaled nitric oxide, eosinophils and total IgE. Shown are comparisons of the biomarkers between patients with severe early-onset and adult-onset asthma, with respective p -values. Box plots display the median (line within the box), interquartile range (edges of the box) and extremes (vertical lines). The dashed line shows the cut-off values for the presence of type 2 inflammation according to GINA.² Abbreviations: FeNO, fractional exhaled nitric oxide, IgE, immunoglobulin E and ppb, parts per billion

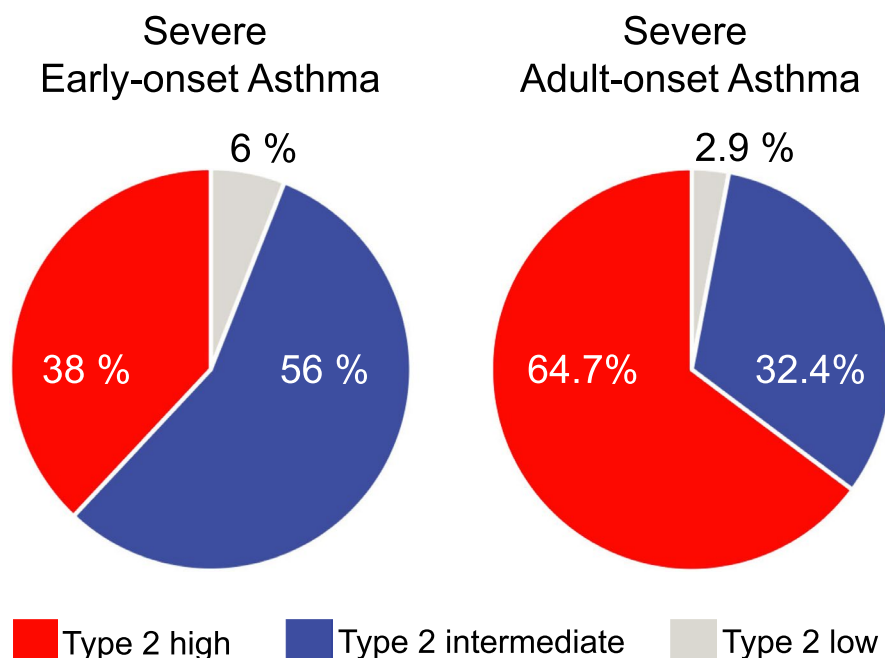


FIGURE 2 Type 2 phenotypes. Shown are type 2 phenotypes of patients with severe early-onset and adult-onset asthma, according to the UKSAR classification.¹ Type 2 high phenotype: ≥ 150 eosinophils/ μ l blood and FeNO ≥ 25 ppb; type 2 low phenotype: < 150 eosinophils/ μ l blood and FeNO < 25 ppb; type 2 intermediate phenotype: either ≥ 150 eosinophils/ μ l blood or FeNO ≥ 25 ppb

from clinical trials,⁶ real-world evidence studies⁷ and current GINA recommendations on the use of biologics.²

Our study revealed a remarkable association of a higher type 2 biomarker expression (FeNO, blood eosinophils) with a lower probability

of allergies (and at least a trend to lower total IgE), both in the comparison between SAA and SEA, and in SAA subgroup analyses. This finding is supported by recent data showing that eosinophilia in patients with SAA is largely independent from IgE-mediated pathways.⁸

However, allergic inflammation can promote NO production and eosinophilia in allergic airway diseases.^{9,10} Therefore, we hypothesize that the intrinsic type 2 inflammation in SAA is stronger than that driven by allergic inflammation in SEA. It needs to be acknowledged that the patients in our cohort had allergies to typical aeroallergens: it cannot be excluded that patients with less common allergies might have a higher type 2 biomarker expression. In addition, one has to bear in mind that blood eosinophils and FeNO values can vary over time and can be substantially influenced by changing doses of ICS.¹¹

It is interesting to note that only a small minority (<10%) of our patients with severe asthma displayed a type 2 low phenotype: this in accordance with data from the UK¹ and Denmark.¹² Therefore, given the ongoing discussion whether 'type 2 low asthma' or 'neutrophilic asthma' exists as a genuine disease entity,¹³ more research is needed to better characterize patients with typical asthma symptoms and low type 2 markers.

CONCLUSION

We compared type 2 biomarker expression between severe early-onset asthma (SEA: age of onset <18 years) and severe adult-onset asthma (SAA: age of onset ≥18 years) in 220 patients (not treated with biologics) routinely referred to a tertiary asthma centre (Rostock, Germany). We demonstrate that SAA is characterized by higher FeNO values (median: 41 vs. 20 ppb, $p < .001$) and higher blood eosinophils (median: 500 vs. 350 eosinophils/ μ l, $p = .01$) than SEA. Accordingly, a type 2 high phenotype (≥ 150 eosinophils/ μ l blood and FeNO ≥ 25 ppb) is more prevalent in SAA than in SEA (64.7% vs. 38%, $p = .002$). Thus, we conclude that SAA is characterized by a stronger type 2 phenotype than SEA, suggesting that the age of onset might be a helpful clinical information for the identification of targeted treatments.

FUNDING INFORMATION

None.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The authors report no conflicts of interest regarding this report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Type 2 biomarker expression (FeNO and blood eosinophils) is higher in severe adult-onset than in severe early-onset asthma

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ONLINE SUPPLEMENTARY MATERIAL

PATIENTS AND METHODS

We analysed data from patients who presented routinely to a specialised severe asthma outpatient clinic in Rostock (Germany) for the evaluation of additional treatment options (especially biologics), after referral by respiratory specialists in the years 2013-2020. Patients were included if they (1) were at least 18 years of age, (2) had a physician diagnosed asthma and a typical history of asthma symptoms, (3) had partly or uncontrolled asthma according to the GINA classification, despite regular inhalation and a good inhaler technique (4) were not currently treated with a biologic (for at least 6 months), (5) fulfilled the criteria for severe asthma (at the time of presentation or during follow-up), (6) had all biomarkers, lung function parameters and clinical information recorded at the day of their first presentation. Patients with a smoking history of more than 10 pack years were only included in this analysis if they had (1) a classic history of asthma (e.g. recurrent night-time symptoms, a substantial variability of symptoms over time, recurrent symptoms after exposure to specific stimuli or a sudden onset of respiratory symptoms), (2) a typical clinical response to inhaled and/or systemic glucocorticoids and (3) no relevant COPD component, as judged by the respective physician. Severe asthma was defined according to the ERS/ATS guideline ¹. Patients not presenting with high-dose ICS treatment at first presentation were included in this analysis if (1) they were continuously treated with oral corticosteroids, (2) their asthma could not be controlled with high-dose ICS treatment and a second controller during follow-up in our department, (3) could be controlled with high-dose ICS treatment and a second controller during follow-up, but worsened on ICS tapering. The research was conducted according to the principles of the World Medical Association Declaration of Helsinki.

Lung function was measured using body plethysmography, carbon monoxide (CO) diffusion capacity measured using the single breath method (Masterscreen, Jaeger, Carefusion, Hoechberg, Germany). Total serum IgE was measured using the UniCAP 100 System, as described by the manufacturer (Thermo Scientific, Braunschweig, Germany). Total and differential blood cell counts were analyzed using standard hematological procedures and a dedicated analyzer (XE 2100, Sysmex, Norderstedt, Germany). Fractional exhaled NO (FeNO) was measured using NIOX VERO, as described by the manufacturer (Circassia AG, Bad Homburg, Germany). According to the UK Severe Asthma Registry (UKSAR) ², a type 2 high phenotype was defined as: ≥ 150 eosinophils / μl blood and FeNO ≥ 25 ppb, a type 2 low phenotype as: <150 eosinophils / μl blood and FeNO < 25 ppb. The type 2 intermediate phenotype was defined by the detection of either ≥ 150 eosinophils / μl blood or FeNO ≥ 25 ppb. Presence of type 2 inflammation (GINA) was defined as: ≥ 150 eosinophils/ μl blood and/or FeNO ≥ 20 ppb and/or a history of clinically allergen-driven symptoms ³. Statistical analysis was performed using SPSS Statistics (Version 20, IBM, Armonk, NY, USA). The majority of parameters was not normally distributed. Therefore, parameters were expressed as medians (minimum – maximum). For the comparison of groups with continuous parameters, the Mann-Whitney-U test was used. Boxplots display the median (line within the box), interquartile range (edges of the box) and extremes (vertical lines). For the comparison of groups with dichotomous parameters, binary logistic regression analysis was performed. Correlation analyses were performed using Spearman's correlation coefficient. Probability values of $p<0.05$ were regarded as significant.

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Clinical characteristics	Severe Early-onset asthma (n = 50)	Severe Adult-onset asthma (n = 170)	p value
Partly controlled / Uncontrolled [GINA]	22.0 %/ 78.0 %	22.4 % / 77.6 %	0.96
% females	44.0 %	50.0 %	0.46
Age at symptom onset [years]	7 (1 - 17)	43 (18 - 81)	<0.001
Age at presentation [years]	51 (19 - 84)	61 (29 - 88)	<0.001
Duration of the disease [years]	41 (10 - 81)	12 (0 - 65)	<0.001
Weight [cm]	85 (50 - 153)	81 (44 - 141)	0.21
Height [kg]	1.75 (1.55 - 1.93)	1.72 (1.50 - 1.96)	0.09
BMI [kg/m ²]	27 (15 - 45)	27 (13 - 41)	0.65
% of patients with BMI ≥ 30	34.0 %	30.6 %	0.67
% Current Smokers	12.0 %	7.6 %	0.34
% Ex-Smokers	32.0 %	50.0 %	0.03
Pack years, PY	0 (0 - 50)	5 (0 - 100)	0.03
% of pts with ≥ 10 PY	24.0 %	44.1 %	0.01
% of pts with any upper airway disease	52.0 %	61.8 %	0.22
% of pts with history of nasal polyps	36.0 %	45.9 %	0.22
% of pts with history of AIT	24 %	7.1 %	0.001
SABA use [puffs per day]	2 (0 - 15)	2 (0 - 20)	0.90
% of pts with exacerbations [last year]	94.0 %	95.3 %	0.71
No. of exacerbations per year	2 (0 - 12)	4 (0 - 15)	0.01
% of pts with continuous OCS therapy	18.0 %	35.3 %	0.02
% of pts with an ICS	100.0 %	98.8 %	1.00
% of pts with high dose ICS [GINA]	70.0 %	61.2 %	0.26
% of pts with a LABA	100.0 %	96.5 %	0.99
% of pts with a LAMA	62.0 %	66.5 %	0.51
% of pts with a LTRA	40.0 %	34.1 %	0.45
% of pts with Theophylline	16.0 %	11.8 %	0.43

Table S1. Clinical characteristics of the patients

Biomarkers	Severe Early-onset asthma (n = 50)	Severe Adult-onset asthma (n = 170)	p value
Blood eosinophils [%]	5.1 (0.0 - 14.3)	5.8 (0.0 - 44.0)	0.38
Blood eosinophils [cells/ μ l]	350 (0 - 1360)	500 (0 - 9370)	0.04
% of pts with ≥ 150 eosinophils/ μ l blood	90.0 %	87.1 %	0.61
% of pts with ≥ 300 eosinophils/ μ l blood	54.0 %	69.4 %	0.06
% of pts with ≥ 600 eosinophils/ μ l blood	22 %	41.2 %	0.02
Total IgE in serum [IU/ml]	361 (4 - 5000)	213 (3 - 6027)	0.14
% of pts with total IgE ≥ 100 IU/ml	76.0 %	71.8 %	0.55
% of pts with any clinically reported allergy	80.0 %	29.4 %	<0.001
FeNO [ppb]	20 (5 - 141)	41 (5 - 232)	<0.001
% of pts with FeNO ≥ 20 ppb	50.0 %	83.5 %	<0.001
% of pts with FeNO ≥ 25 ppb	42.0 %	75.3 %	<0.001
% of pts with FeNO ≥ 50 ppb	22.0 %	41.8 %	0.01
Type 2 inflammation present [GINA]	96.0 %	99.4 %	0.11
Type 2 high phenotype [UKSAR]	38.0 %	64.7 %	0.002
Type 2 low phenotype [UKSAR]	6.0 %	2.9 %	0.32
Lung function			
FEV ₁ [% predicted]	62 (24 - 119)	60 (16 - 129)	0.96
% of pts with FEV ₁ $\leq 80\%$ predicted	76.0 %	77.6 %	0.78
FEV1 % FVC	65 (34 - 91)	67 (34 - 99)	0.62
Residual volume [RV] [% predicted]	143 (60 - 353)	144 (52 - 312)	0.99
% of pts with RV $\geq 150\%$ predicted	40.0 %	42.4 %	0.87
DLCO % predicted	85 (34 - 108)	79 (32 - 138)	0.21
% of pts with DLCO $\leq 60\%$ predicted	8.0 %	14.1 %	0.42
% of pts with DLCO $\leq 40\%$ predicted	6.0 %	3.5 %	0.55
KCO % predicted	103 (41 - 141)	102 (40 - 152)	0.67

Table S2. Type 2 biomarkers and lung function

Severe adult-onset asthma: Clinically reported allergies	Allergies (n = 50)	No Allergies (n = 120)	p value
Blood eosinophils [cells/ μ l]	410 (0 - 3800)	500 (0 - 9370)	0.69
FeNO [ppb]	31 (7 - 146)	47 (5 - 232)	0.06
Total IgE in serum [IU/ml]	371 (8 - 6027)	152 (3 - 5000)	0.006
Type 2 high phenotype [UKSAR]	50.0 %	70.0 %	0.03
Severe adult-onset asthma: General smoking history	Never-Smokers (n = 72)	Ever-Smokers (n = 98)	
Blood eosinophils [cells/ μ l]	540 (10 - 3570)	470 (0 - 9370)	0.74
FeNO [ppb]	45 (7 - 182)	40 (5 - 232)	0.65
Total IgE in serum [IU/ml]	179 (3 - 6027)	221 (8 - 5000)	0.36
Type 2 high phenotype [UKSAR]	68.1 %	68.0 %	0.44
Severe adult-onset asthma: Cumulative smoke exposure	< 10 pack years (n = 95)	$\geq$ 10 pack years (n = 75)	
Blood eosinophils [cells/ μ l]	500 (0 - 9370)	500 (0 - 3620)	0.89
FeNO [ppb]	46 (7 - 182)	39 (5 - 232)	0.32
Total IgE in serum [IU/ml]	196 (3 - 6027)	221 (8 - 5000)	0.84
Type 2 high phenotype [UKSAR]	67.4 %	61.3 %	0.49
Severe adult-onset asthma: Gender	Females (n = 85)	Males (n = 85)	
Blood eosinophils [cells/ μ l]	550 (0 - 3620)	420 (0 - 9370)	0.12
FeNO [ppb]	38 (5 - 182)	45 (7 - 232)	0.20
Total IgE in serum [IU/ml]	164 (8 - 6027)	259 (3 - 5000)	0.32
Type 2 high phenotype [UKSAR]	67.1 %	62.4 %	0.47
Severe adult-onset asthma: Age of asthma onset	18 - 40 years (n = 78)	> 40 years (n = 92)	
Blood eosinophils [cells/ μ l]	470 (0 - 3570)	500 (0 - 9370)	0.46
FeNO [ppb]	38 (6 - 182)	46 (5 - 232)	0.46
Total IgE in serum [IU/ml]	198 (3 - 6027)	215 (8 - 5000)	0.25
Type 2 high phenotype [UKSAR]	64.1 %	65.2 %	0.92

Severe adult-onset asthma: Body mass index (BMI)	BMI < 30 kg/m² (n = 118)	BMI ≥ 30 kg/m² (n = 52)	
Blood eosinophils [cells/μl]	520 (0 - 9370)	460 (10 - 3800)	0.37
FeNO [ppb]	40 (5 - 232)	43 (7 - 144)	0.35
Total IgE in serum [IU/ml]	253 (3 - 6027)	141 (10 - 5000)	0.14
Type 2 high phenotype [UKSAR]	66.1 %	63.5 %	0.69
Severe adult-onset asthma: Continuous OCS treatment	OCS (n = 60)	No OCS (n = 110)	
Blood eosinophils [cells/μl]	319 (0 - 3800)	530 (10 - 9370)	<0.001
FeNO [ppb]	40 (5 - 144)	41 (7 - 232)	0.26
Total IgE in serum [IU/ml]	150 (7 - 3517)	250 (3 - 6027)	0.04
Type 2 high phenotype [UKSAR]	51.7 %	71.8 %	0.02
Severe adult-onset asthma: History of nasal polyps	Nasal polyps (n = 78)	No nasal polyps (n = 92)	
Blood eosinophils [cells/μl]	605 (0 - 2889)	415 (0 - 9370)	0.02
FeNO [ppb]	39 (7 - 182)	41 (5 - 232)	0.73
Total IgE in serum [IU/ml]	153 (3 - 5000)	233 (7 - 6027)	0.57
Type 2 high phenotype [UKSAR]	69.2 %	60.9 %	0.26

Table S3. Type 2 biomarkers in severe adult-onset asthma: subgroup analyses

TABLE LEGENDS

Table S1. Clinical characteristics

Shown are median values (minimum-maximum) for continuous variables or percentages (%) for dichotomous variables, including respective p values. *Abbreviations denote:* Allergen Immunotherapy (AIT), Global Initiative for Asthma (GINA), Long-acting beta-agonist (LABA), Long-acting muscarinic antagonist (LAMA), Leukotriene receptor antagonist (LTRA), Inhaled corticosteroid (ICS), Oral corticosteroid (OCS), Patients (pts), Pack years (PY), Short-acting beta-agonist (SABA).

Table S2. Type 2 biomarkers and lung function

Shown are median values (minimum-maximum) for continuous variables or percentages (%) for dichotomous variables, including respective p values. *Abbreviations denote:* Diffusion capacity for carbon monoxide (DLCO), carbon monoxide transfer coefficient (KCO), Fraction of exhaled nitric oxide (FeNO), Forced expiratory volume in the first second (FEV₁), Forced vital capacity (FVC), Immunoglobulin E (IgE), Patients (pts), Parts per billion (ppb), Residual volume (RV).

Table S3. Type 2 biomarkers in severe adult-onset asthma: subgroup analyses

Shown are median values (minimum-maximum) for continuous variables or percentages (%) for dichotomous variables (including respective p values) in subgroups of the patients with severe adult-onset asthma. *Abbreviations denote:* Body mass index (BMI), Fractional exhaled nitric oxide (FeNO), Immunoglobulin E (IgE), Parts per billion (ppb).