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The Influence of Emphysema on Treatment Response to Biologic Therapy in Severe Asthma

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Background: Patients with severe asthma (SA) benefit from biologic therapy substantially. However, the impact of smoking-related comorbidities remains unclear due to the exclusion of patients with ≥10 pack-years from asthma studies. Our aim was to examine the effects of emphysema on biologic treatment response in SA in this retrospective cohort study.

Methods: Pulmonary emphysema was examined using computed tomography. Patients with SA were included and divided into two groups based on emphysema quantity (≥5% or <5%). They received either anti-IgE (22.1%), anti-IL-5-(receptor) (52.3%), or anti-IL-4/IL-13 (25.6%) biologic therapy. Treatment response was assessed after 7.8 ± 2.5 months based on acute exacerbations (AE), oral corticosteroid (OCS) therapy, Asthma Control Test (ACT), forced expiratory volume in 1 second (FEV1) and using the Biologics Asthma Response Score (BARS).

Results: This study comprised 86 patients (mean age 56.1 ± 12.8 years; 54% female). Half (43, 50.0%) were never-smokers, half ex-smokers with an average of 26.9 ± 18.2 pack-years. Patients with ≥5% emphysema were more often ex-smokers (80% vs 41%, p=0.002), had poorer lung function (FEV1 median 1.3 [interquartile range: 1.0;1.6] vs 1.8[1–2;2.4] L, p=0.037), and more comorbid COPD (50% vs 21%, p=0.012). However, no significant differences were noted in treatment response regarding annualized AE rate (−2.5[−5;-1] vs −3.0[−5;-2] n/year, p=0.295) and OCS reduction (−4[−10;0] vs −5[−10;0] mg, p=0.691), ACT score (5[3;9] vs 4[0;9] points, p=0.579) or FEV1 improvement (0.03[−0.15;0.25] vs 0.23[−0.5;0.49] L, p=0.052), BARS (p=0.312), and remission rates (15.0% vs 19.7%, p=0.753).

Conclusion: In patients with severe asthma, those with comorbid emphysema show similar treatment response to biologic therapy. Therefore, suitable patients should not be denied biologics due to the presence of emphysema.

Keywords: severe asthma, emphysema, smoking, biologic therapy

Introduction

Severe asthma is a chronic respiratory condition characterized by persistent airway inflammation and airflow limitation that remains inadequately managed even with optimized therapy (high-dose inhaled corticosteroids (ICS) plus another bronchodilatator), or that deteriorates when high-dose treatment is reduced.[1] The development of biologic therapies has revolutionized the management of severe asthma.[2] Biologic therapy has shown significant efficacy in improving asthma control, reducing exacerbations, and enhancing lung function.[2,3] However, since current- or ex-smokers ≥10 pack-years have been excluded from clinical trials,[4–8] there is limited evidence regarding the influence of smoking-related comorbidities, such as emphysema, on the response to biologic therapy in patients with severe asthma. Recent studies have demonstrated that prior smoking exposure does not significantly impact the response to biologic treatments in patients with severe asthma, regardless of the specific biologic therapy used.[9–11] Similar findings have been reported in cases of asthma comorbid with chronic obstructive pulmonary disease (COPD).[12] However, it is noteworthy that for

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COPD Dupilumab is the only biologic that has been robustly shown to reduce exacerbations and has recently been approved for this indication.[13,14] Pulmonary emphysema, commonly associated with COPD, is also a significant smoking-related comorbidity of asthma associated with increased morbidity and mortality.[15–17] Despite its clinical relevance, there is a paucity of research specifically addressing the efficacy of biologic therapies in asthma patients with coexisting emphysema. Therefore, further investigation is warranted to better understand this interaction and to optimize therapeutic strategies for this specific patient population.

This study aimed to quantify the extent of lung emphysema using computer tomography (CT) and investigate its influence on biologic treatment response in asthma patients. By elucidating the impact of emphysema on treatment outcomes, we aim to provide valuable insights into the management of severe asthma patients with concurrent emphysema.

Methods

Study Design and Patient Population

This study is a retrospective cohort study conducted at the Department of Internal Medicine II – Pneumology Department, University Hospital Bonn in Germany. The study was approved by the local ethics committee (No. 174/22). All participants provided written informed consent for the register study of the German Asthma Net (GAN).

The study included a total of 86 consecutive patients with a diagnosis of severe asthma, based on the Global Initiative for Asthma recommendations, who were eligible for biologic therapy.[1] The inclusion criteria for this study were the presence of a native CT of the thorax, a diagnosis of severe asthma, biologic therapy eligibility and a follow-up after at least 3 months of biologic therapy. Exclusion criteria included patients under 18 years of age. Due to the exploratory nature of this study, all consecutive patients in the given time period were included which fulfilled the inclusion criteria, to obtain the greatest cohort possible. Our hypothesis was that the presence of pulmonary emphysema has no significant influence on the treatment response to biologic therapy.

Assessment of Emphysema

Data for this study were obtained from patient medical records from 2017 to 2022. The extent of lung emphysema was quantified by experienced radiologists using non-contrast chest CT scans obtained as part of routine clinical practice with multidetector CT scanners (≥128 rows). The emphysema analysis was performed using a commercially available software (IMPAX, Agfa HealthCare N.V., Mortsel, Belgium). An example of emphysema quantification on a patient with 32% pulmonary emphysema, visible as red areas, is shown in Figure 1. Consistent with established practice, emphysema was defined as lung parenchyma with attenuation values of less than −950 hounsfield units at inspiration.[18–20] For each CT dataset, an emphysema ratio was generated, which is defined as the percentage of lung volume with emphysema divided by total lung volume.

To evaluate treatment response relative to emphysema severity within our cohort, patients were divided into two groups. As no recommendations for a cut-off for clinically meaningful emphysema exists, we chose the 5% threshold based on existing literature[21–23] and studies where this specific cutoff has been employed.[24,25] We additionally applied a 10% emphysema cut-off for further validation of our results.

Treatment and Outcome Measures

All patients underwent biologic therapy according to the standard treatment guidelines.[26] The choice of biologic therapy was based on individual patient characteristics and physician discretion. The outcome measures to assess the effectiveness of the treatment approach included changes in the number of annualized acute exacerbations (AE), reduction of maintenance oral corticosteroid (OCS) doses, asthma control assessed by the Asthma Control Test (ACT) and forced expiratory volume in 1 second (FEV1). The evaluation of treatment response was conducted after the closest possible time point to 6 months (at least 3 months), to adequately address reduction of exacerbations and oral corticosteroid therapy (OCS). The number of acute exacerbations up to the follow-up point was extrapolated to an annualized

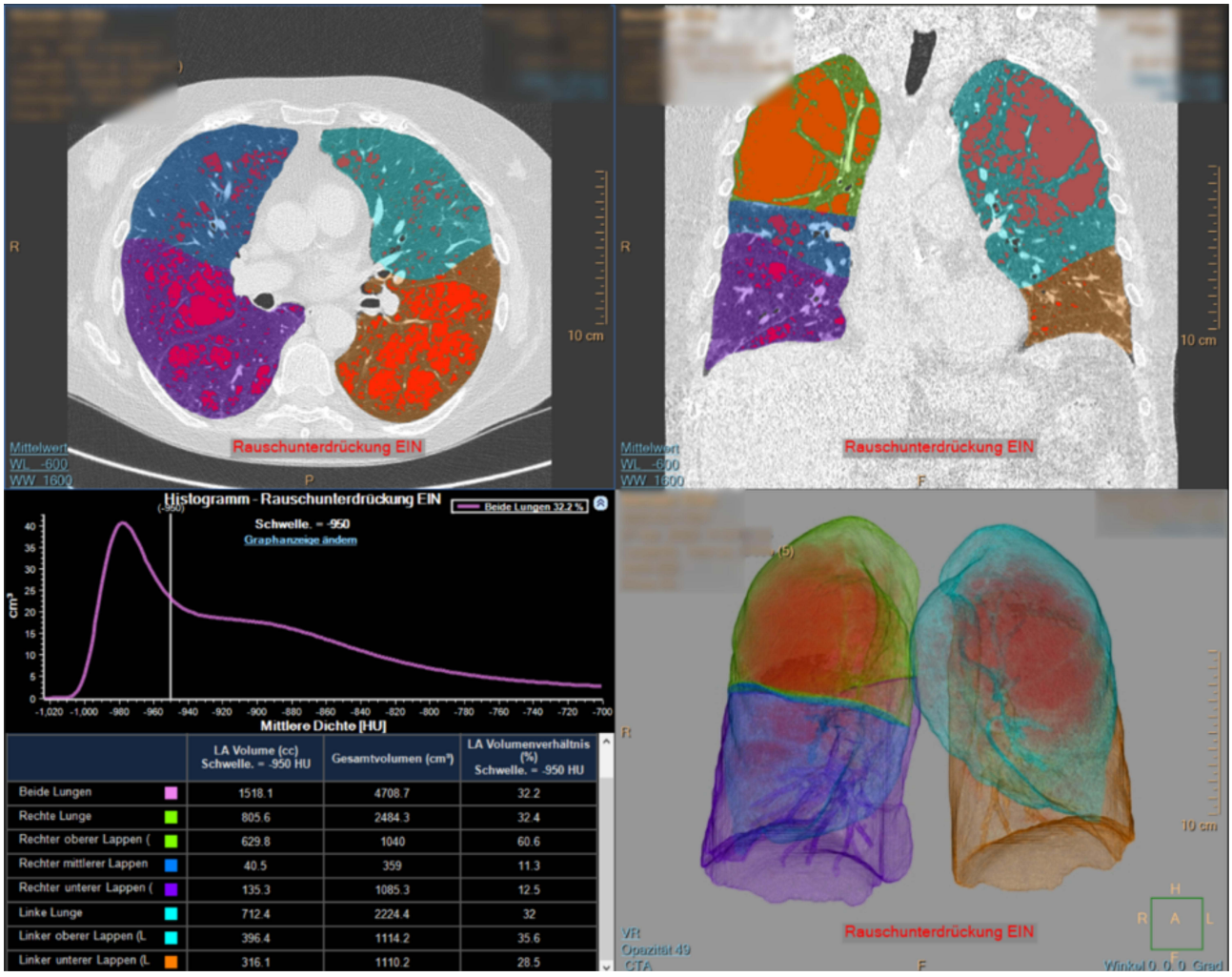

Figure 1 Example of Emphysema Quantification in IMPAX Software. The figure showcases a representative image or screenshot captured within the software interface. This patient was a 65-year-old female with 32 pack years, late onset asthma and a comorbid emphysema occupying 32% of her lungs. The red markings represent areas of emphysematous change within the lungs.

exacerbation rate in 12 months, to meet standardized end-points as suggested by the ATS/ERS statement on endpoints for asthma trials and clinical practice.[27]

Additionally, the Biologics Asthma Response Score (BARS) was utilized. BARS incorporates ACT-score, acute exacerbation rate and reduction in OCS dose to evaluate treatment response, allowing for an assessment of whether there was a "good response", "response" or "inadequate response" overall.[28]

Asthma remission was defined as an absence of acute exacerbations, the absence of an oral corticosteroid therapy, a good asthma control defined by an ACT score ≥20 points and a stable lung function (FEV1), according to the German guidelines.[26]

Information on the patient history, eg, comorbidities or allergies (positive sensitization, clinically apparent), were obtained from the patients' medical history files. Biomarkers, especially blood eosinophil count, were obtained from the closest timepoint before biologic therapy initiation, without the influence of OCS therapy and outside of an exacerbation.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 28. Due to the small sample size of the respective groups, non-parametric Mann–Whitney-*U*-test was used for metric data, if not stated otherwise. Nominal or ordinal-scaled data were analyzed by Pearson's chi-squared test or Fisher's exact test when applicable. For some variables data

are missing for some patients, the numbers of available data are individually stated in the results table for each variable. The A p-value less than 0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

A total of 86 patients diagnosed with severe asthma were enrolled in this study, with a mean age of 56.1 ± 12.8 years. Among these, 54 (62.8%) were female. 50% were never-smokers, 50% ex-smokers. No patients were current smokers at the beginning of biologic therapy. Physician-diagnosed COPD was present in 24 patients (27.9%). Patients with a smoking history had an average of 26.9 ± 18.2 pack-years. Additionally, those with a smoking history exhibited a significantly higher amount of emphysema (6.6 ± 8.6%) compared to never-smokers (1.5 ± 1.8%) ($p<0.001$).

Patients had a native CT Thorax scan within 9 ± 29.5 month of beginning biologic therapy. The range of emphysema severity spanned from 0.0% to 36.1%. Among the patient cohort, the majority (77%) had less than 5% pulmonary emphysema, 10 individuals (11.6%) had ≥10% emphysema, of which 3 (3.48%) displayed ≥20% emphysema, all of whom had a history of smoking (as depicted in Figure 2).

At the commencement of biologic therapy, nearly all patients were receiving maximal inhaled therapy, including high-dose ICS, LAMA, and LABA. The distribution of used biologics and the exposure to prior biologics were similar in both groups. Among the cohort of 30 patients with previous biologic therapy, 15 patients (17.4%) received one prior biologic, 13 patients (15.1%) two, and two patients (3.5%) received three prior biologics. The assessment of therapy response according to BARS aimed to compare patient parameters post-therapy with those observed prior to previous antibody treatments.

Baseline Characteristics Based on Emphysema Stratification

Within the group with ≥5% emphysema, a significantly higher proportion were ex-smokers compared to the group with <5% emphysema (80.0% vs 40.9%, p=0.002). Furthermore, the ≥5% emphysema group had a significantly greater pack-year history and demonstrated worse pulmonary function, as evidenced by, eg, worse median FEV1 values of 1.34 [1.0;1.6] compared to 1.8 [1.3;2.4] liters (p=0.037), median diffusion capacity (DLCO) of 52 [21;60] vs 78 [61;87] % predicted (p=0.028) or signs of hyperinflation (RV % predicted; 169 [153;181] vs 157 [119;182], p=0.037). Accordingly, the group with emphysema ≥5% included a significantly higher number of patients with pre-diagnosed COPD (50.0% vs 21.1%, p=0.012).

Both groups did not exhibit significant differences in asthma-specific biomarkers like FeNO (37 [14;77] vs 27 [16;66] ppB, p=0.866), blood eosinophil count (300 [129;510] vs 450.0 [210;720] /µL, p=0.627) and IgE-levels (156 [90;382] vs 238 [87;504] U/mL, p=0.588), or asthma comorbidities like chronic rhinosinusitis with nasal polyps or allergies. All baseline characteristics comparing both groups are presented at Table 1.

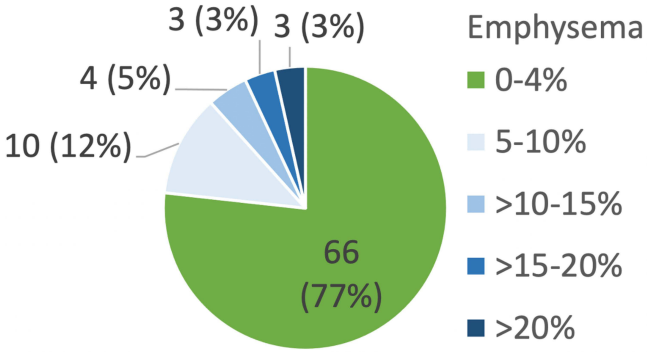

Figure 2 Distribution of Patients Across Emphysema Severity Groups. The pie chart illustrates the distribution of patients categorized into specific groups based on the percentage of emphysema severity. Each segment of the pie represents the percentage of patients falling within defined ranges of emphysema severity.

Table 1 Baseline Characteristics

	n	Emphysema <5% n = 66	Emphysema ≥5% n = 20	p-value
Age	86	57 [50;63]	65 [52;69]	0.085
Sex (male)	86	24 (36.4%)	8 (40.0%)	0.768
BMI (kg/m^2)	86	28 [26;32]	27 [23;31]	0.357
Years since diagnosis		24 [10;39]	22 [10;39]	0.443
Biologic therapy in history	86	24 (36.4%)	6 (30.0%)	0.601
Emphysema (%)	86	0.9 [01;2.3]	10.5 [6.7;18.1]	**<0.001***
ACT Score	83	10 [7;13]	10 [6;13]	0.716
Acute exacerbations (n/year)	86	4 [3;7]	5 [3;6]	0.295
Medications				
ICS	86	66 (100%)	20 (100%)	-
LAMA	86	63 (95.5%)	20 (100%)	1.000
LABA	86	66 (100%)	20 (100%)	-
Maintenance OCS	86	47 (71.2%)	13 (65%)	0.596
OCS dose (mg)[a]	60	5 [4;10]	7.5 [4;15]	0.260
Theophylline		2 (3.0%)	1 (5.0%)	0.553
Biologic therapy				
Omalizumab	86	15 (22.7%)	4 (20.0%)	1.000
Dupilumab	86	18 (27.3%)	4 (20.0%)	0.514
Mepolizumab	86	10 (15.2%)	6 (30.0%)	0.188
Benralizumab	86	23 (34.8%)	6 (30.0%)	0.688
Smoking status	86			
Never-smokers		39 (59.1%)	4 (20.0%)	**0.002***
Ex-smokers		27 (40.9%)	16 (80.0%)	**0.002***
Pack-years	86	0 [0;20]	15 [7;38]	0.004*
Pulmonary function				
FEV_1 (L)	86	1.8 [1.3;2.4]	1.3 [1.0;1.6]	**0.037***
FEV_1 (% of predicted)	86	63 [45;75]	51 [37;57]	**0.007***
FEV1/FVC (%)	84	72 [60;81]	62 [50;73]	**0.007***
TLC (% of predicted)	84	105 [88;117]	100 [97;122]	0.410
VC (L)	85	2.7 [2.0;3.4]	2.1 [1.9;2.8]	0.121
VC (% of predicted)	85	75 [64;92]	70 [52;84]	0.135
RV (% of predicted)	85	157 [119;182]	169 [153;181]	**0.037***
R_{tot} (% of predicted)	84	165 [112;209]	213 [154;290]	0.263
DLCO (% of predicted)	62	78 [61;87]	52 [21;60]	**0.028***
DLCO/VA (% of predicted)	62	78 [62;87]	69 [36;96]	0.238
Biomarkers				
Eos (n/µL)	86	450.0 [210;720]	300 [129;510]	0.627
FeNO (ppB)	66	27 [16;66]	37 [14;77]	0.866
IgE (U/mL)	86	238 [87;504]	156 [90;382]	0.588
Comorbidities				
Allergies	86	51 (77.3%)	14 (70.0%)	0.557
COPD	86	14 (21.2%)	10 (50%)	**0.012***
CS with nasal polyps	86	12 (18.2%)	2 (10.0%)	0.505
CS without nasal polyps	86	11 (16.7%)	2 (10.0%)	0.724
Urticaria	86	5 (7.6%)	0 (0.0%)	0.586

(*Continued*)

Table 1 (Continued).

	n	Emphysema <5% n = 66	Emphysema ≥5% n = 20	p-value
Rhinoconjunctivitis	86	16 (24.2%)	3 (15.0%)	0.542
GERD	86	13 (19.7%)	5 (25.0%)	0.754
EGPA	86	6 (9.1%)	1 (5.0%)	1.000

Notes: The data are represented as n (%) or median [interquartile range]. * and bold font = significant p-value of p<0.05. [a] = including only individuals with OCS therapy (mg prednisolone-equivalent).

Abbreviations: ACT, Asthma Control Test; BMI, Body mass index, COPD, Chronic obstructive pulmonary disease; CS, Chronic sinusitis; DLCO, Diffusing capacity of the lungs for carbon monoxide; DLCO/VA, DLCO divided by alveolar volume (transfer coefficient); EGPA, Eosinophilic granulomatosis with polyangiitis; Eos, Eosinophil granulocytes in blood; FeNO, Fractional exhaled nitric oxide; FEV1, Forced expiratory volume in 1 second; FEV1/FVC (Tiffeneau Index), Ratio of the FEV1 to the forced vital capacity of the lungs; GERD, Gastroesophageal reflux disease; ICS, Inhaled Corticosteroids; IgE, Immunoglobulin E levels in blood; KCO, Carbon monoxide transfer coefficient; L, liters; LABA, Long-acting beta-agonist; LAMA, Long-acting muscarinic antagonist; OCS, Oral Corticosteroids; pO2, Partial pressure of oxygen; TLC, Total lung capacity; VC, Vital capacity; RV, Residual volume; Rtot, Total airway resistance.

Treatment Response

After a follow-up time of 7.8 ± 2.5 months, a good treatment response could be shown for both groups, presenting in a reduction of acute exacerbations to 0 [0;2] in both groups (p=0.236), and a reduction of OCS dose to 0 [0;6.5] and 0

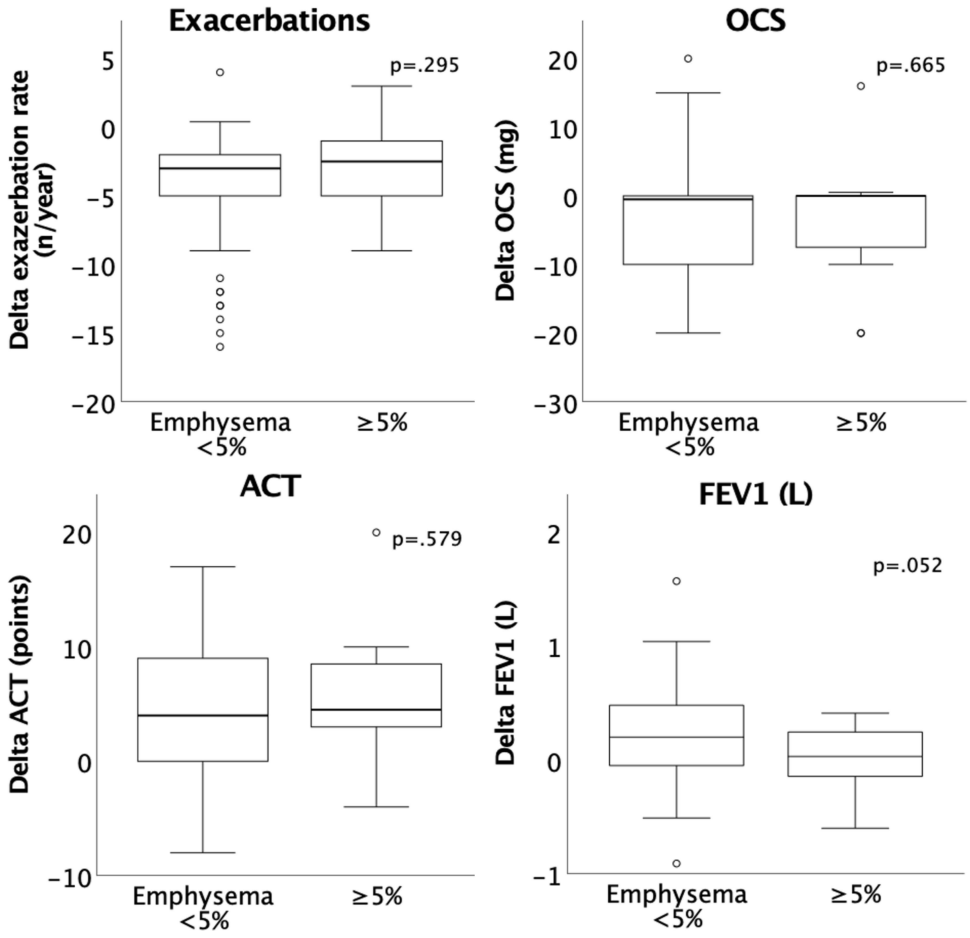

Figure 3 Comparison of Treatment Response Measures Based on Emphysema Severity. Four boxplots representing treatment response measures concerning varying degrees of emphysema severity. Each boxplots displays the change from baseline to follow-up for the specific treatment response parameters, categorized by emphysema severity (<5% and ≥5%). The p-values were acquired with the Mann–Whitney-U test.

Abbreviations: FEV1, Forced Expiratory Volume in 1 second (FEV1) improvement; ACT, Asthma Control Test (ACT) score increase; OCS, Oral Corticosteroid (OCS) use reduction.

Table 2 Follow-Up

Variable	n	Emphysema <5% n = 66	Emphysema ≥5% n = 20	p-value
Follow-up duration (months)	86	8 [6;10]	7.5 [6.25;9.75]	0.951
Acute exacerbations (n/year)	86	0 [0;2]	0 [0;2]	0.236
OCS dose (mg)[a]	86	0 [0;5]	0 [0;6.5]	0.644
ACT score (points)	83	15.0 [10;22]	17.0 [10;21]	0.798
FEV_1 (L)	85	2.1 [1.5;2.5]	1.3 [1.1;1.7]	**<0.001***
FEV_1 (% of predicted)	85	66 [53;81]	52 [36;61]	**<0.001***
Change in acute exacerbations (n/year)	86	−3.0 [−5;-2]	−2.5 [−5;-1]	0.295
Change in OCS-dose (mg)	60	−5 [−10;0]	−4 [−10;0]	0.691
Change in ACT-score (points)	83	4 [0;9]	5 [3;9]	0.579
Change in FEV_1 (L)	85	0.23 [−0.5;0.49]	0.03 [−0.15;0.25]	0.052
Change in FEV_1 (% of predicted)	85	8 [−2;16]	1 [−4;9]	0.069
Remission	86	13 (19.7%)	3 (15.0%)	0.753[f]
BARS	86			0.312[f]
Good therapy response		34 (52%)	12 (60%)	
Therapy response		24 (36%)	4 (20%)	
Insufficient therapy response		8 (12%)	4 (20%)	
Discontinuation of therapy	15			
Switch due to adverse effects		3 (4.5%)	1 (5%)	1.000 [f]
Switch due to non-efficacy		3 (4.5%)	1 (5%)	1.000 [f]
Discontinuation due to adverse effects		2 (3%)	1 (5%)	0.553 [f]
Discontinuation due to non-efficacy		3 (1.5%)	1 (5%)	1.000 [f]
Results with cut-off 10% emphysema				
Variables	**n**	**Emphysema <10% n = 76**	**Emphysema ≥10% n = 10**	**p-value**
Change in FEV_1 (L)	85	0.18 [−0.07;0.48]	0.02 [−0.21;0.27]	0.195
Change in ACT-score (points)	83	5 [0;9]	6 [0;9]	0.453
Change in OCS-dose (mg)[+]	60	−5 [−10;0]	−2.5 [−14;0.25]	0.621
Change in acute exacerbations (n/year)	86	−3 [−6;-2]	−1.4 [−3.5;-1]	**0.033***
Remission	86	14 (18.4%)	2 (20.0%)	1.000 [f]
BARS	86			0.801[f]
Good therapy response		41 (53.9%)	5 (50%)	
Therapy response		25 (32.9%)	3 (30%)	
Insufficient therapy response		10 (13.2%)	2 (20%)	
Discontinuation or switch of therapy	15			0.467 [f]
Due to adverse events		7 (9.2%)	0 (10%)	
Due to non-efficacy		6 (9.2%)	2 (10%)	

Notes: The data are represented as n (%) or median [interquartile range]. * and bold font = significant p-value of <0.05. [f] = Fisher's exact test. [a] = including only individuals with OCS therapy (mg prednisolone equivalent).

Abbreviations: ACT, Asthma Control Test; BARS, Biologic Asthma Response Score; FEV_1, Forced expiratory volume in 1 second; L, liters; OCS, Oral Corticosteroids.

[0;5] mg, respectively (p=0.664). ACT score improved similarly, exceeding the minimal-clinical important difference of 3 points.

There were no significant differences in treatment response between the two groups. In detail, there was no difference in the reduction of annualized acute exacerbations (−2.5 [−5;-1] vs −3.0 [−5;-2] n/year, p=0.236), reduction of OCS doses (−4 [−10;0] vs −5 [−10;0] mg, p=0.691), ACT improvement (5 [3;9] vs 4 [0;9], p=0.579) or FEV1 improvement (0.03 [−0.15;0.25] vs 0.23 [−0.5;0.49] L, p=0.052). Results are depicted as boxplots in Figure 3 and at Table 2.

Regarding BARS, 60 vs 52% of all patients in each group reached a good therapy response, while 20%, respectively, 12% had an insufficient therapy response (p=0.312, Table 2). The rate of patients who changed or ended biologic therapy due to adverse events or non-efficacy was comparable between patients with ≥5% or <5% emphysema (16.7% vs 20.0%, Table 2).

The rate of asthma remission was comparable with 15.0% in the ≥5% emphysema group and 19.7% in the <5% emphysema group (p=0.753).

Similar results were seen if an emphysema cut-off of 10% was applied, except the reduction in acute exacerbation rate was more pronounced in the group with <10% emphysema (−1.4 [−3.5;-1] vs −3 [−6;-2] n/year, p=0.003, Table 2).

Of the three patients with a pronounced pulmonary emphysema of >20%, two showed a therapy response, while one did show an insufficient therapy response, according to BARS.

Thus, our analysis suggests that patients with severe asthma and comorbid pulmonary emphysema show a similar treatment response compared to those without emphysema.

Discussion

As a central result, we show that the presence of a pulmonary emphysema does not significantly impact the success of biologic therapy in this patient group.

While usually clinical asthma studies exclude patients with >10 pack-years of smoking history, this does not reflect the real-world asthma patient collective. In fact, nearly half of the adult asthmatic population in most developed countries are current or former smokers.[16] The GAN (German Asthma Network) study found 2.7% of the asthma patients recruited into the registry in Germany were current smokers and 43.6% ex-smokers.[29,30] Existing literature suggests the coexistence of COPD and emphysema in patients with asthma correlates with decreased survival rates and presents clinical challenges.[15] Notably, half of the patients in our collective had a smoking history, and, as anticipated, these individuals showed a significantly higher degree of emphysema compared to never-smokers.[31] A subset of patients in our study even exhibited a substantial burden of emphysema, with 11.6% presenting with ≥10% emphysema. This in turn underscores the clinical relevance of considering emphysema in the management of severe asthma.

Nonetheless, irrespective of the presence of concurrent emphysema, both patient groups exhibited a similar favorable response to biologic therapy. Additionally, the rates of both remission and treatment discontinuation were comparable. The low rate of patients with asthma remission in the emphysema group may be contributed to persisting symptoms caused by the comorbid emphysema, which cannot be expected to be addressed by biologic therapy.

The fact that the analysis with a 10% emphysema cut-off yielded comparable results, and that two of the three patients with a pulmonary emphysema of >20% showed a response to biologic therapy, supports the notion that biologic therapy was successfully treating the asthma component, regardless of the comorbid emphysema. While it is noteworthy to reiterate the group with ≥10% emphysema showed a significantly lower reduction of acute exacerbations, which may be due to more pronounced comorbid smoking-related lung-injury, it is as important to be cautious whilst interpreting these findings due to the small sample size of this subgroup consisting of only 10 patients. Our previous research had yielded similar outcomes for asthma patients with significant smoking exposure, regardless of the presence of emphysema.[10] We attributed this outcome to the careful patient selection process employed to determine eligibility for biologic therapy.

The therapeutic effects of biologic therapy with anti-IL5-/ anti-IL5-receptor-therapy showed only a marginal reduction in exacerbation rates among patients with COPD who did not have concurrent asthma.[32,33] In contrast, the recent BOREAS and NOTUS studies demonstrated a 30% and 34% reduction in acute exacerbations of COPD patients with type-2-Inflammation by anti-IL-4/13-therapy, which has now led to the approval of the medication for COPD.[13,14] It can be assumed biologic therapy has a favoring effect on type-2-inflammation, regardless of the underlying obstructive disease. In this way, the concept of anti-inflammatory disease-modifying anti-asthmatic drugs (DMAADs) has emerged in asthma therapy, with a clear focus on airway inflammation.[34] This raises the question of whether the focus should shift towards detecting treatable traits, such as type-2-inflammation in obstructive lung diseases, rather distinction between asthma and COPD. However, with Tezepelumab there is now an effective therapy option regardless of the presence of type-2-inflammation.[34] Moreover, in cases of inadequate therapeutic response, switching to another biologic is an

effective and often necessary option in asthma, whereas this option is currently not (yet?) available for COPD.[35] Therefore, precise diagnosis and phenotyping remains crucial for optimizing therapy, as does gaining further insights into the efficacy of biologic therapy across different patient groups.

A subgroup analysis regarding the effectiveness of different biologics in our patient population is not feasible due to the small size of the subgroups.

We hence propose that biologic therapy represents a valuable treatment option for individuals with severe asthma, even those with concurrent emphysema, provided that patient selection is conducted carefully. It remains imperative to manage comorbid COPD and emphysema as distinct, but possibly concurrent clinical entities, which also includes designation of the two entities (as opposed to the term "asthma-COPD-overlap (ACO)".

While the influence of emphysema on treatment response was a central focus of our investigation, it is noteworthy that we observed no significant differences in biomarkers associated with severe asthma among our patient groups. These biomarkers, ie, IgE, FeNO, and blood eosinophil count, are crucial indicators of the underlying inflammatory processes and disease activity.[26,36] Previous research has demonstrated varying results regarding airway inflammation markers in relation to smoking status; some studies have reported reduced sputum eosinophil counts and lower levels of fractional exhaled nitric oxide (FeNO) in active smokers. In certain cases, former smokers have exhibited signs of induced type-2 inflammation. Collectively, these findings exhibit an inconsistent nature of the observed associations between smoking and airway inflammation markers.[1,37–39] Accordingly, there was no difference in other phenotype defining characteristics, like the presence of allergies or CRSwNP as comorbidities. This suggests that while emphysema may indeed present clinical challenges and complexities in the management of severe asthma, it may not substantially alter the inflammatory pathways, disease activity or comorbidities that are commonly associated with the primary condition. This is a possible explanation for the good therapy response, despite comorbid emphysema. On the other hand, patients with a relevant smoking history and/or the presence of pulmonary emphysema may have been preferably selected to be eligible for biologic therapy, when said inflammation markers or comorbidities were present.

Our findings indicate that the presence of pulmonary emphysema should not hinder biologic therapy in suitable patients with severe asthma. This supports an inclusive approach to treatment eligibility.

Regarding patients with more severe emphysema are needed to fully assess its impact on treatment response and provide more evidence for clinical decision-making.

As this study was conducted at a single center and included only ambulatory patients who had undergone native CT scans, this study had its limitations as it might have introduced preselection bias. Furthermore, the selection of the threshold 5% for clinically relevant emphysema was guided by existing literature.[21–25] However, it's important to note that, to date, universally accepted and validated cut-off values for this purpose remain lacking. Additionally, there were no expiratory CT scans available, therefore the amount of hyperinflation in both asthma and comorbid COPD might have been underestimated. However, the conduction of expiratory CT scans are not part of the clinical routine, and therefore may provide rather theoretical implications.

Furthermore, the study's sample size was relatively small, and the patient cohort exhibited significant variability in the extent of emphysema. While there was a subset of patients with substantial emphysema, the majority had less severe emphysema. This imbalance in patient distribution might limit the ability to draw robust conclusions about the impact of severe emphysema on treatment response. Additionally, the use of a calculated annualized exacerbation rate does present a potential for error; however, after a median follow-up of nearly 8 moths, we believe that the therapeutic response can be assessed with sufficient accuracy. Remission status on the other hand has to be interpreted with caution, as remission can only be assessed after 12 months by definition. Furthermore, an inadequate choice of biologic may also have influenced the therapy response. However, only a small number of patients discontinued therapy due to lack of efficacy.

The observational nature of the study restricts the ability to establish causality. Retrospective analyses rely on existing data that were collected for various clinical purposes, which may not be as comprehensive or consistent.

Nonetheless, this study possesses several key strengths enhancing the credibility and significance of its findings. The use of real-world data reflects the actual clinical practice and treatment outcomes in a diverse patient population, thereby enhancing the study's external validity. The quantitative assessment of emphysema extent using computed tomography (CT) enables a standardized and objective measure of emphysema severity.

Conclusion

In conclusion, our study shows a good treatment response to biologic asthma therapy, regardless of the presence of emphysema. Careful patient selection and individualized treatment decisions are crucial in optimizing treatment outcomes in this patient population. Concurrent emphysema should not hinder biologic therapy in suitable patients with severe asthma.

Abbreviations

ACT, Asthma Control Test; ACO, Asthma-COPD-overlap; AE, Acute exacerbations; BARS, Biologic Asthma Response Score; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; CS, Chronic sinusitis; DLCO, Diffusing capacity of the lungs for carbon monoxide; DLCO/VA, DLCO divided by alveolar volume (transfer coefficient); EGPA, Eosinophilic granulomatosis with polyangiitis; Eos, Eosinophil granulocytes in blood; FeNO, Fractional exhaled nitric oxide; FEV1, Forced expiratory volume in 1 second; FEV1/FVC (Tiffeneau Index), Ratio of the FEV1 to the forced vital capacity of the lungs; GAN, German Asthma Net; GERD, Gastroesophageal reflux disease; ICS, Inhaled Corticosteroid; IgE, Immunoglobulin E serum levels; KCO, Carbon monoxide transfer coefficient; L, liters; LABA, Long-acting beta-agonist; LAMA, Long-acting muscarinic antagonist; OCS, Oral Corticosteroids; pO2, Partial pressure of oxygen; TLC, Total lung capacity; VC, Vital capacity; RV, Residual volume; Rtot, Total airway resistance.

Data Sharing Statement

All Data are available from the corresponding author upon request.

Ethics Approval and Consent

All participants provided written informed consent for the German Asthma Net (GAN) registry. The study was approved by the responsible local ethics committee of the University of Bonn, confirming its adherence to the principles outlined in the Declaration of Helsinki and compliance with all the federal and local requirements (No. 174/22).

Consent for Publications

The authors provide their consent for the publication of the study results.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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