Original Article

Response to Biologics and Clinical Remission in the Adult German Asthma Net Severe Asthma Registry Cohort

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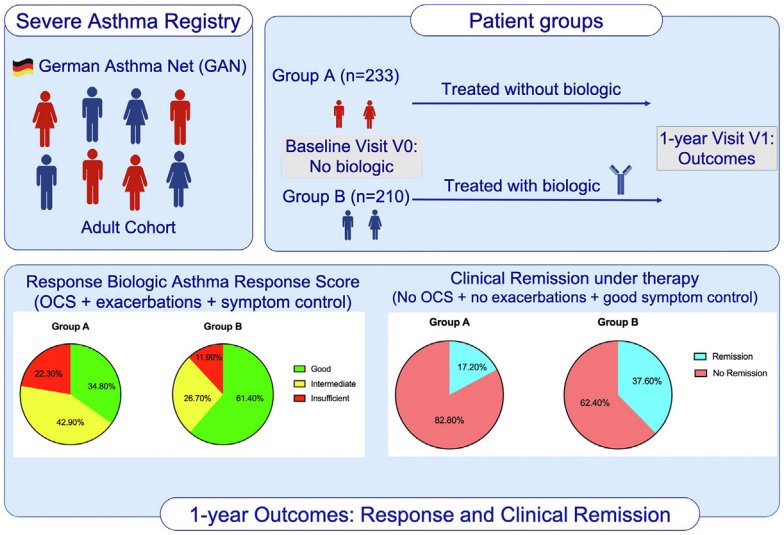
What is already known about this topic? Clinical remission on treatment, defined as more than 1 year of good symptom control in the absence of exacerbations and oral corticosteroid therapy, has recently been proposed as a possible treatment goal even in severe asthma.

What does this article add to our knowledge? It provides first real-life data from a severe asthma cohort, showing a remission rate of one-third after start of a biologic. Patients treated without a biologic had lower remission rates despite less severe disease at baseline.

How does this study impact current management guidelines? Clinical remission can be achieved in a proportion of patients with severe asthma, and the concept might help improve outcomes in the future; biologics are an important factor for achieving remission.

VISUAL SUMMARY



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Abbreviations used
ACQ-6- 6-item Asthma Control Questionnaire
ACT- Asthma Control Test
BARS- Biologic Asthma Response Score
BEC- blood eosinophil count
GAN- German Asthma Net
ICS- inhaled corticosteroid
OCS- oral corticosteroid

BACKGROUND: Recently, criteria for evaluation of response to biologics have been proposed and the concept of clinical remission has gained attention as a possible goal even in severe asthma.
OBJECTIVE: To analyze the response and remission in the German Asthma Net severe asthma registry cohort.
METHODS: We included adults not using a biologic at baseline (V0) and compared patients treated between V0 and 1-year visit (V1) without using a biologic (group A) to patients starting with a biologic after V0 and continuing it up to V1 (group B). We applied the Biologics Asthma Response Score to quantify composite response in good, intermediate, or insufficient. We defined clinical remission (R) as absence of significant symptoms (Asthma Control Test score ≥ 20 at V1) in the absence of exacerbations and oral corticosteroid therapy.
RESULTS: Group A included 233 and group B 210 patients, the latter receiving omalizumab (n = 33), mepolizumab (n = 40), benralizumab (n = 81), reslizumab (n = 1), or dupilumab (n = 56). At baseline, group B had less often an allergic phenotype (35.2% vs 41.6%), lower Asthma Control Test score (median, 12 vs 14), more exacerbations in the past year (median, 3 vs 2), and more often high-dose inhaled corticosteroid treatment (71.4% vs 51.5%) than group A. After 1 year of treatment, rates of response (good: 61.4% vs 34.8%; intermediate: 26.7% vs 42.9%; insufficient: 11.9% vs. 22.3%) and/or clinical remission (37.6% vs 17.2%) were higher in group B than in group A.
CONCLUSIONS: Despite more severe asthma at baseline, patients treated with biologics had a markedly higher probability of achieving good clinical response and/or remission than patients treated without biologics. **(J Allergy Clin Immunol Pract 2023;■:■-■)**

Key words: *Severe asthma; Treatment; Biologic; Response; Remission; Exacerbations; OCS use; Asthma control; Pulmonary function*

INTRODUCTION

Biologic treatments have improved outcomes in severe asthma, including reductions in oral corticosteroid (OCS) use and exacerbations as well as improvements in symptoms and lung function achieved, both in randomized controlled trials[1-8] and in real-life cohorts.[9-14]

Although many patients who receive biologics for severe asthma experience clinically meaningful improvements, others do not respond sufficiently. So far, assessment of response to biologics has not been standardized and different definitions of response have been proposed recently.[12,15-18] The Biologic Asthma Response Score (BARS) has been developed as a simple tool for composite response assessment in routine clinical practice using the main criteria exacerbations, OCS therapy, and symptoms and the optional criterion pulmonary function (Milger et al[19]; Figure 2). The score defines good, intermediate, and insufficient response and aims to support the decision

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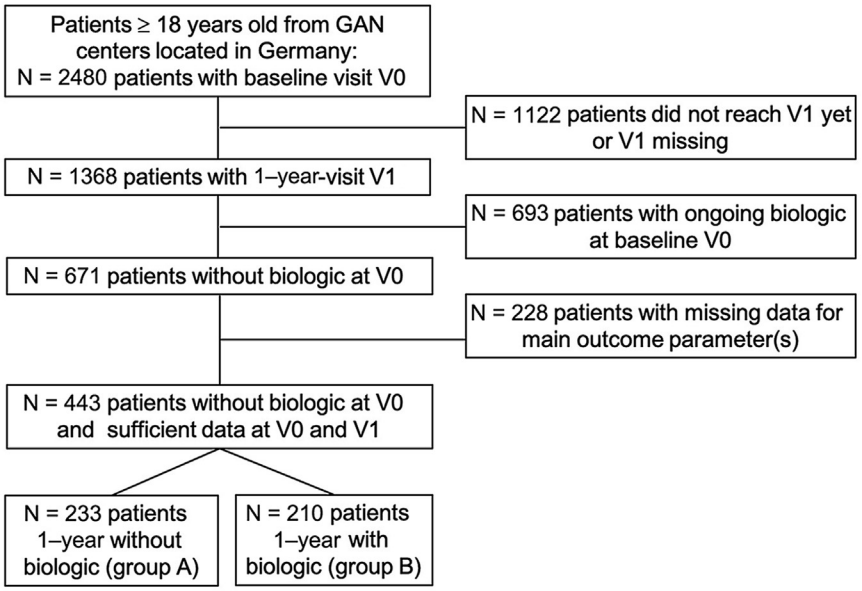


FIGURE 1. Patient cohort (Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] flowchart).

whether an ongoing biological therapy should be continued, switched, or stopped.

Furthermore, the concept of clinical remission on treatment has been proposed and gained attention as a treatment goal, even in severe asthma.[20] The term "disease-modifying antiasthmatic drugs" was proposed for any drug class that can potentially achieve the goal of asthma remission (including inhaled corticosteroids [ICSs], allergen immunotherapy, and biologics).[21]

Asthma remission can occur spontaneously, after treatment (eg, allergen immunotherapy), or on treatment (eg, biologics).[21,22] It is currently under discussion whether the term asthma remission should include an improvement in lung function (eg, increase of ≥100 mL in FEV_1)[20] or not.[21] However, there is consensus that there are 3 clinical cornerstones of asthma remission: good asthma symptom control, absence of exacerbations, and no need for systemic steroid treatment for asthma for a period of at least 1 year.[21,22] Currently, data on clinical remission rates in real-life patients with severe asthma on treatment with biologics are scarce. Moreover, the criteria for remission and response to biologics are still incompletely defined. Therefore, we asked whether patients with severe asthma achieve a good response and clinical remission in real-life and what is the role of biologics in reaching these goals. We compared 1-year outcomes of patients from the German Asthma Net (GAN) severe asthma cohort who were newly initiated with a biologic to patients who did not receive a biologic in the first year after inclusion in the registry. Furthermore, we aimed to elucidate which parameters are associated with achievement of remission using regression analyses of baseline variables.

METHODS

The GAN Severe Asthma Registry is prospectively collecting routine clinical parameters of patients with severe asthma (European Respiratory Society/American Thoracic Society definition[23]) at baseline and annual follow-ups as described previously.[24] All patients provided written informed consent before participation in the registry, which was approved by the Ethics Committee of the University of Mainz and local institutional review boards at each institution and is performed in accordance with the principles of the Declaration of Helsinki. Data were extracted on July 22, 2022, and for this study we selected all patients from the registry who:

- were 18 years or older at inclusion (baseline visit V0) and inscribed at GAN centers in Germany.
- had sufficient data at V0 and after 1 year (V1) including the 4 main outcome parameters: exacerbations, OCS use, Asthma Control Test (ACT) score, and FEV_1.
- did not use biologics at V0.
- either started a biologic after V0 and continued it up to 1 year (visit V1 [group B]), or were treated without using a biologic from V0 up to V1 (group A).

Patients already receiving a biologic at the time of inclusion in the registry were ruled out. Patient selection is visualized in Figure 1.

Phenotypes

Asthma phenotypes given in Table I are those the treating physician coded according to *International Classification of Diseases, Tenth Revision* code German version: J45.0 predominantly allergic asthma, J45.1 nonallergic (intrinsic) asthma, J45.8 mixed forms (allergic and nonallergic). These are clinical diagnoses focusing on the main triggers of asthma. Physicians take into account biomarker levels for classification, but there are no formal biomarker thresholds.

Prescription of biologics

Treating physicians prescribed biologics in clinical routine according to German health care guidelines (Nationale Versorgungsleitlinie Asthma) and licensing criteria of each drug. All biologics are covered by the statutory health insurance. Nationale Versorgungsleitlinie defines severe asthma in adults when under high-dose inhaled ICS and use of at least 1 additional controller or oral corticosteroid for more than 6 months a year, at least 1 of the following characteristics is present (or would be present if therapy was reduced): (1) obstructive ventilatory defect FEV_1 less than 80%

TABLE I. Baseline characteristics at V0 in patients subsequently treated with biologic and without biologic

Item	Category	Group A without biologic (N = 233)	Group B with biologic (N = 210)	*P* value
Sex: female, n (%)		140 (60.1)	113 (53.8)	.18*
Age (y), mean ± SD		53.7 ± 12.5	55.4 ± 13.0	.11†
BMI (kg/m^2), mean ± SD		27.4 ± 6.3	28.1 ± 6.2	.35†
Duration of asthma (y), mean ± SD		20.6 ± 15.1	20.9 ± 16.3	.96†
Age at onset (y), median		30.3 (18.9)	32.9 (19.9)	.24†
Age group at onset (y), n (%)	Early (<12 y)	67 (28.8)	48 (23.0)	.17*
	Late (>12 y)	166 (71.2)	161 (77.0)	
Asthma phenotype *ICD-10*, n (%)	Predominantly allergic asthma	97 (41.6)	74 (35.2)	**.0109***
	Nonallergic (intrinsic) asthma	78 (33.5)	56 (26.7)	
	Mixed forms of asthma (allergic and nonallergic)	58 (24.9)	80 (38.1)	
Exacerbations in the last 12 mo	None	9 (3.9)	10 (4.8)	**.0062**†
	1×/y	58 (24.9)	25 (11.9)	
	>1×/y, but <1×/mo	148 (63.5)	158 (75.2)	
	≥1×/mo	18 (7.7%)	17 (8.1)	
Exacerbations in the last 12 mo at V0, median (IQR)		2 (1-4)	3 (2-5)	**.0003**†
ACT score, median (IQR)		14 (10-18)	12 (9-16)	**.0189**†
ACT score: level of control, n (%)	<16 (uncontrolled) 16-19 (partially controlled) ≥20 (controlled)	143 (61.4) 45 (19.3) 45 (19.3)	150 (71.4) 31 (14.8) 29 (13.8)	.08*
ACQ-6 score, median (IQR)		2.80 (1.8-3.8)	3.20 (2.0-4.2)	**.0131**†
Incapacity to work, n (%)	Yes	45 (19.3)	29 (13.8)	.46*
Smoking habits, n (%)	Never-smoker	130 (55.8)	114 (54.3)	.95*
	Active smoker	4 (1.7)	4 (1.9)	
	Former smoker	99 (42.5)	92 (43.8)	
Former smoker: pack-years, median (IQR)		9 (2-18.8)	10 (3-15)	.72†
Active smoker: pack-years, median (IQR)		16.3 (10-27.5)	20.0 (11.6- 28.5)	.88†
Comorbidities, n (%)				
Allergic rhinitis	Yes	124 (53.7)	109 (51.9)	.71*
Atopic dermatitis	Yes	24 (10.4)	18 (8.6)	.52*
Food allergy	Yes	55 (23.8)	44 (21.0)	.47*
Nasal polyps	Yes	45 (36.9)	70 (40.9)	.48*
Chronic rhinosinusitis	Yes	101 (43.3)	109 (51.9)	.07*
EGPA	Yes	2 (0.9)	9 (4.3)	**.0206***
COPD	Yes	12 (5.2)	14 (6.7)	.49*
Medication				
Daily OCS, n (%)		85 (36.5)	82 (39.0)	.58*
Daily OCS dosage (mg) (prednisolone equivalent), median (IQR)		10.0 (5-20)	7.5 (5-15)	.18†
High-dose ICS, n (%)		120 (51.5)	150 (71.4)	**.0001***
Medium-dose ICS, n (%)		72 (30.9)	43 (20.5)	
LABA, n (%)		221 (94.8)	205 (97.6)	.13*
LAMA, n (%)		110 (47.2)	168 (80.0)	**<.0001***
LTRA, n (%)		76 (32.6)	89 (42.4)	**.0338***
Theophylline, n (%)		33 (14.2)	17 (8.1)	**.0439***
GINA step treatment level, n (%)	3‡	31 (13.3)	12 (5.7)	**.0003***
	4	45 (19.3)	22 (10.5)	
	5	157 (67.4)	176 (83.8)	

(continued)

TABLE I. *(Continued)*

Item	Category	Group A without biologic (N = 233)	Group B with biologic (N = 210)	*P* value
Type of biologic started after V0, n (%)				
Mepolizumab		0	40 (19.0)	
hereof off-label			1 (2.5)	
reslizumab		0	1 (0.5)	
hereof off-label			0	
benralizumab		0	81 (38.5)§	
hereof off-label			2 (2.5)	
dupilumab		0	56 (26.6)§	
hereof off-label			1 (1.8)	
omalizumab		0	33 (15.7)	
hereof off-label			10 (30.3)	
Pulmonary function, mean ± SD				
FEV_1 % predicted		67.5 ± 20.8	64.4 ± 20.1	.13†
FEV (L)		1.96 ± 0.72	1.95 ± 0.75	.85†
FVC % predicted		81.5 ± 17.8	79.1 ± 18.0	.11†
FVC (L)		2.91 ± 0.91	2.95 ± 0.93	.74†
FEV/FVC × 100%		61.5 ± 22.7	64.5 ± 16.4	.64†
RV % predicted		150.4 ± 37.5	151.4 ± 50.5	.73†
RV (L)		2.92 ± 0.79	3.15 ± 1.23	.48†
R tot (kPa × s/L)		0.51 ± 0.38	0.51 ± 0.34	.74†
MEF 25% predicted, mean ± SD		47.4 ± 30.8	39.3 ± 30.4	**.0016**†
Biomarkers				
Blood eosinophils (/μL), median (IQR)		241 (89-500)	364 (173-677)	**.0002**†
		N = 146	N = 180	
Blood eosinophils threshold, n (%)	<150/μL	54 (37.0)	38 (21.1)	**.0003***
	150-300/μL	32 (21.9)	43 (23.9)	
	>300/μL	60 (41.1)	99 (55.0)	
FENO (ppb), median (IQR)		35.0 (14-53)	37 (20-73)	**.02**†
		N = 95	N = 138	
FENO threshold	<25 ppb	37 (38.9)	41 (29.7)	**.02***
	≥25 ppb	58 (61.1)	97 (70.3)	
		N = 95	N = 138	
Total IgE (IE/mL), median (IQR)		178 (54-447)	166 (60-392)	.75†
		N = 90	N = 133	
Total IgE thresholds	<100 IE/mL	31 (34.4)	48 (36.1)	
	≥ 100 IE/mL	59 (65.6)	85 (63.9)	
		N = 90	N = 133	
Any specific sensitization (prick or specific IgE), n (%)	Yes	172 (79.6)	161 (78.5)	.78*
	No	44 (20.4)	44 (21.5)	
	Missing value	N = 17	N = 5	

COPD, Chronic obstructive pulmonary disease; *EGPA*, eosinophilic granulomatosis with polyangiitis; *FENO*, fractional exhaled nitric oxide; *GINA*, Global Initiative for Asthma; *IQR*, interquartile range; *LABA*, long-acting β-agonist; *LAMA*, long-acting muscarinergic agonist; *LTRA,* leukotriene receptor antagonist; *MEF 25%*, maximal expiratory flow at 25% of vital capacity; *ppb*, parts per billion; *RV*, residual volume.

Values meeting significance level of $P < .05$ are highlighted in bold.

*P value group A vs group B by χ^2 test.

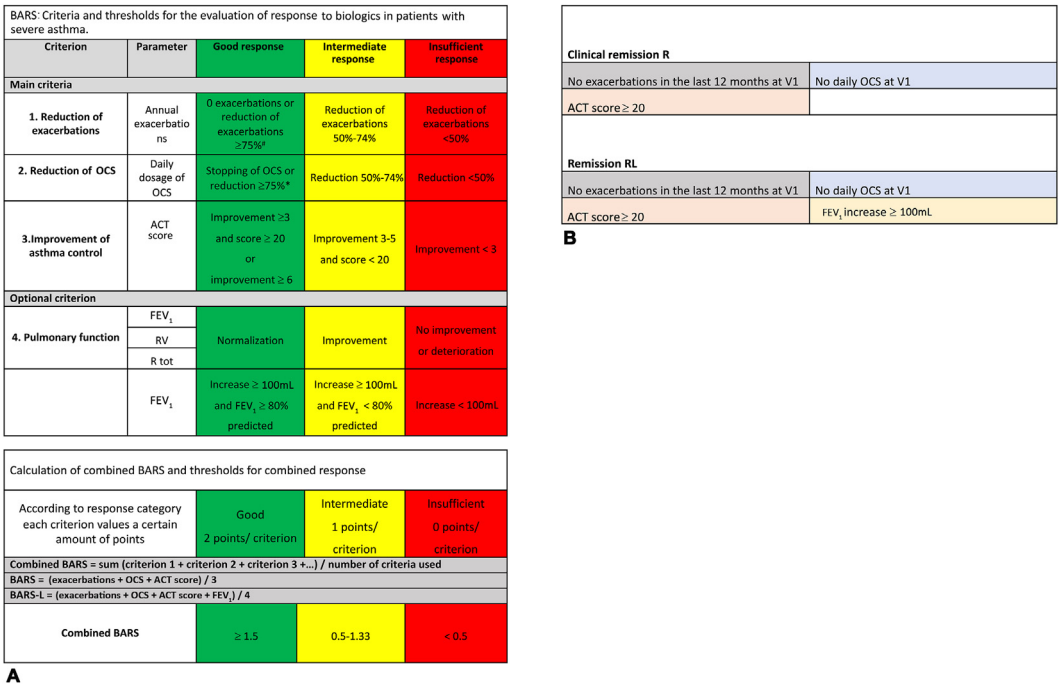
†P value group A vs group B by U test.

‡Patients formally classified as GINA 3 due to low-dose ICS but who needed intense treatment with multiple controllers, mostly quadruple therapy with ICS + LABA + LAMA + LTRA were included here.

§One patient received benralizumab and dupilumab at the same time, thus total number of patients is 210, while number of biologics was 211.

predicted and FEV_1/FVC less than lower limit of normal (LLN); (2) frequent exacerbations: 2 or more OCS therapies needed in the last 12 months; (3) severe exacerbations: 1 or more exacerbation with hospital treatment or ventilation in the last 12 months; (4) partially controlled or uncontrolled symptoms.

Additional prescription criteria exist for each biologic as follows: *Benralizumab*: Severe eosinophilic asthma with blood eosinophils greater than or equal to 300/μL, or if under OCS therapy greater than or equal to 150/μL. *Dupilumab*: Severe asthma with type 2 inflammation with fractional exhaled nitric oxide greater than or



BARS: Criteria and thresholds for the evaluation of response to biologics in patients with severe asthma.

Criterion	Parameter	Good response	Intermediate response	Insufficient response
Main criteria				
1. Reduction of exacerbations	Annual exacerbations	0 exacerbations or reduction of exacerbations ≥75%#	Reduction of exacerbations 50%-74%	Reduction of exacerbations <50%
2. Reduction of OCS	Daily dosage of OCS	Stopping of OCS or reduction ≥75%*	Reduction 50%-74%	Reduction <50%
3.Improvement of asthma control	ACT score	Improvement ≥3 and score ≥ 20 or improvement ≥ 6	Improvement 3-5 and score < 20	Improvement < 3
Optional criterion				
4. Pulmonary function	FEV_1	Normalization	Improvement	No improvement or deterioration
	RV			
	R tot			
	FEV_1	Increase ≥ 100mL and FEV_1 ≥ 80% predicted	Increase ≥ 100mL and FEV_1 < 80% predicted	Increase < 100mL

Calculation of combined BARS and thresholds for combined response

According to response category each criterion values a certain amount of points	Good 2 points/ criterion	Intermediate 1 points/ criterion	Insufficient 0 points/ criterion
Combined BARS = sum (criterion 1 + criterion 2 + criterion 3 +...) / number of criteria used			
BARS = (exacerbations + OCS + ACT score) / 3			
BARS-L = (exacerbations + OCS + ACT score + FEV_1) / 4			
Combined BARS	≥ 1.5	0.5-1.33	< 0.5

A

Clinical remission R	
No exacerbations in the last 12 months at V1	No daily OCS at V1
ACT score ≥ 20	
Remission RL	
No exacerbations in the last 12 months at V1	No daily OCS at V1
ACT score ≥ 20	FEV_1 increase ≥ 100mL

B

FIGURE 2. Definitions of response and remission. (**A**) BARS: First, each response criterion is categorized into good, intermediate, or insufficient response. Each criterion in category good values 2 points, intermediate 1 point, insufficient 0 point. Then, the combined BARS is calculated by summing the points and subsequently dividing by the number of criteria. (**B**) Clinical remission (R) and including FEV_1 (RL). Remission is achieved only if all the given criteria are fulfilled; otherwise, the patient is classified as no remission. *RV*, residual volume, R tot, total airway resistance.

equal to 25 parts per billion and/or blood eosinophils greater than or equal to 150/μL. *Mepolizumab*: Severe eosinophilic asthma with increased blood eosinophils greater than or equal to 150/μL. *Omalizumab*: Severe allergic asthma with sensitization to a perineal allergen and total IgE within the dose range. In the few patients who fulfilled the definition of severe asthma but did not fulfill biomarker requirements, off-label use was granted: Benralizumab (n = 2), dupilumab (n = 1), mepolizumab (n = 1), and omalizumab (n = 5 [seasonal allergens but no perineal one] and n = 5 [total IgE level higher than dosing table]; highest recommended dose was applied). Doses and intervals of biologics were as recommended in the European Medicines Agency prescription information, with omalizumab dose between 75 mg and 600 mg every 2 or 4 weeks according to body weight and total IgE, mepolizumab 100 mg every 4 weeks, benralizumab 30 mg every 4 weeks for 3 times and then every 8 weeks, reslizumab intravenous every 4 weeks with 3 mg/kg body weight, and dupilumab 300 mg (in patients with OCS) and 200 mg (in patients without OCS) every 2 weeks.

Definition of response

We used the BARS for assessment of treatment response after 1 year. It uses the main criteria—reduction in exacerbations, reduction in daily OCS dose, improvement in asthma control (ACT score)—and we named the combined score of these 3 items as BARS and the 4-criteria score including FEV_1 as BARS-L. Thresholds for each criterion define good, intermediate, and insufficient response, which value 2, 1, and 0 points for each criterion, respectively (Figure 2, *A*). Normalization of FEV_1 was defined as an increase in FEV_1 of greater than or equal to 100 mL to greater than or equal to 80% predicted when the baseline value was less than 80% predicted. To calculate the combined score, points of all criteria are summed and then divided by the number of criteria. Thresholds for the combined score are greater than or equal to 1.5 for good, 0.5 to 1.33 for intermediate, and less than 0.5 for insufficient response.

A criterion may be not applicable when no further improvement from baseline is possible (eg, when the patient did not use any daily OCS at baseline) or less often did not have any exacerbations at baseline because of high daily OCS use, or already had normal pulmonary function at baseline ($FEV_1 \geq 80\%$ predicted). In this case, the criterion is disregarded (no points given and the number of criteria used as devisor is reduced accordingly).

Definition of remission

Clinical remission "R" was defined as ACT score of 20 or more in the absence of exacerbations in the last 12 months while taking no daily OCS (Table I). Furthermore, we analyzed another definition of remission using the additional criterion of FEV_1 improvement of greater than or equal to 100 mL "RL."[22]

Statistics

We performed statistical analyses using the statistical software SAS 9.4 (TS1M6) Cary, NC, USA for Microsoft Windows, Redmond, WA, USA. To compare the frequency of parameters between groups A and B, we used a χ^2 test or *U* test for dichotomous or continuous variables, respectively. All statistical tests were 2-sided with a significance level (alpha) of 0.05.

We performed univariate logistic regression analysis with the dependent parameter remission RL and baseline variables (V0) as independent variables (Table II). Furthermore, we selected significant parameters from the univariate analysis, for multivariate logistic regression analysis (Table II).

TABLE II. Outcome criteria and BARS in patients treated with or without a biologic after 1 y (V1)

Outcome at V1	Group A without biologic (N = 233)	Group B with biologic (N = 210)	*P* value
Absolute values at V1			
Exacerbations in the last 12 mo, median (IQR)	1 (0 to 2)	0 (0 to 1)	**.0002***
Patients who stopped OCS therapy before V1, n (% of patients taking OCS at V0)	22 (25.9) $N_{V0} = 85$	43 (52.4) $N_{V0} = 82$	**.0004†**
Daily OCS dosage (mg) (only patients with OCS at V1), median (IQR)	7.5 (5 to 20)	5.0 (4 to 10)	**.0241***
ACT (score), median (IQR)	17 (13 to 21)	20 (15 to 23)	**.0005***
FEV_1 (L), mean ± SD	2.03 ± 0.77	2.25 ± 0.9	**.0212***
Changes at V1 compared with V0			
Exacerbation reduction (%), median (IQR)	−71.8 (−100 to 0)	−100 (−100 to −50)	**<.0001***
OCS dosage reduction (%), median (IQR)	0 (−100 to 0)	−100 (−100 to 0)	**<.0001***
Δ ACT (score), median (IQR)	2 (−1 to 6)	5 (2 to 10)	**<.0001***
Δ FEV_1 (L), mean ± SD	0.15 ± 0.43	0.31 ± 0.6	**.002***
Combined BARS, median (IQR)			
BARS	1.00 (0.5 to 1.5)	1.67 (1 to 2)	**<.0001***
BARS-L	1.00 (1 to 2)	1.50 (1 to 2)	**<.0001***

IQR, Interquartile range.
P values considered significant (<.05) are highlighted in bold.

RESULTS

There were 233 patients in group A and 210 patients in group B (Figure 1). In group B, 58% of the patients were treated with biologics targeting the IL-5 pathway (benralizumab, mepolizumab, reslizumab), whereas 15.7% were treated with omalizumab and 26.6% with dupilumab (Table I). The median duration of biologic treatment at V1 was 11 months (interquartile range, 8-12 months). Several baseline parameters differed significantly between groups A and B (Table I). In group B, there was a lower prevalence of the allergic asthma phenotype (35.2% vs 41.6%), higher exacerbation rates (median, 3 vs 2), and a lower ACT score (median, 12 vs 14; Tables III and IV). Frequencies of comorbidities (including the most prevalent ones: allergic rhinitis and chronic sinusitis) were similar in both groups, while the diagnosis of eosinophilic granulomatosis with polyangiitis was more frequent in group B (4.3% vs 0.9% in group A).

There were no significant differences in pulmonary function parameters, except for lower MEF25 values in group B (39.3% vs 47.4% predicted; Table I). Blood eosinophil counts (BECs, 364 vs 241/μL) and fractional exhaled nitric oxide (37 vs 35 parts per billion) values were higher in group B, whereas IgE levels were similar between the groups (Table I). Frequencies of OCS use and dosage, and the overall frequency of ICS and long-acting β-agonist therapy, were similar in both groups (Table I). However, treatment with high-dose ICSs, long-acting muscarinic antagonists, and leukotriene receptor antagonists as well as with Global Initiative for Asthma step 5 therapy was more prevalent in group B than in group A (Table I).

After 1 year, both groups improved, with greater improvement in group B than in group A regarding annual exacerbations, OCS dose reduction, ACT score improvement, and FEV_1 improvement (Table II, Figure 3). Absolute values at V1 were significantly better for annual exacerbations (0 vs 1), stopping of OCS (52.4% vs 25.9%), ACT score (20 vs 17), and FEV_1 (2.25 vs 2.03 L) in group B than in group A (Table III).

According to BARS, response rates were significantly higher in group B, with 61.4% good, 26.7% intermediate, and 11.9% insufficient response, than in group A (34.8%, 42.9%, and 22.3%, respectively, Figure 3, *E*). Similar results were obtained when including FEV_1 in the analysis (BARS-L, Figure 3, *F*).

Remission occurred more often in group B than in group A, both when using the pure clinical definition (R) (37.6% vs 17.2%) and when using the remission definition with additional lung function improvement (RL) (32.1% vs 9.5%) (Figure 4). Each of the 4 remission criteria was met more frequently in group B (Figure 4, *A-D*). For individual biologics in group B, remission RL was achieved in patients treated with anti-IgE in 14%, with anti−IL-5/R in 38%, and with anti−IL-4R in 23%.

Univariate logistic regression analysis revealed that an age of asthma onset of more than 12 years, higher blood eosinophils, presence of nasal polyps, and use of biologics showed significant positive associations with remission, whereas OCS therapy and dose displayed negative associations with the occurrence of remission (Table III). Because duration of asthma and age at asthma diagnosis (<12 years) were significantly correlated (*U* test, $P < .001$), only the latter was included in multivariate analysis. Multivariate logistic regression analysis showed that no OCS therapy at baseline, higher BEC, and the use of biologics were significantly associated with the occurrence of remission RL after 1 year of treatment (Table IV).

When looking only at patients not treated with biologics (group A alone), we found that remission RL was positively associated with baseline (V0) ACT score and negatively with presence of OCS and Global Initiative for Asthma step 5 treatment in univariate logistic regression analysis (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). In multivariate analysis, higher baseline ACT score and absence of OCS treatment were associated with remission RL (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

Assessment of response to biologics and remission under treatment are current concepts in severe asthma, with their exact definitions still being discussed. We analyzed the frequencies of patients who fulfilled recently proposed definitions of response and remission in a real-life severe asthma cohort.

TABLE III. Univariate logistic regression analysis of remission RL and baseline parameters in the total cohort (group A + group B)

No.	Item	N	Estimate	SE	*P* value	Standardized estimate	Odds ratio	95% CI (Wald) for odds ratio	
								Lower limit	Upper limit
1	Intercept	360	−1.134	0.562					
	Age (y)		−0.003	0.010	.7596	−0.022	0.997	0.978	1.017
2	Intercept	382	−1.461	0.171					
	Sex (male)		0.303	0.253	.2313	0.082	1.353	0.825	2.221
3	Intercept	286	−1.043	0.238					
	Duration of asthma (y)		−0.022	0.011	**.0381**	−0.191	0.978	0.958	0.999
4	Intercept	381	−2.508	0.613					
	Age at asthma diagnosis (>12 y)		0.654	0.330	**.0471**	0.157	1.924	1.008	3.672
5	Intercept	382	−1.291	0.157					
	ICD-10: Allergic asthma		−0.105	0.263	.6904	−0.028	0.901	0.538	1.508
6	Intercept	297	−2.854	0.485					
	Eosinophil threshold (low <150/μL; intermediate 150-300/μL; high >300/μL)		0.729	0.187	**<.0001**	0.344	2.073	1.438	2.989
7	Intercept	211	−1.176	0.231					
	FENO at presentation (ppb)		0.003	0.003	.2733	0.089	1.003	0.997	1.010
8	Intercept	207	−0.962	0.188					
	Total IgE (IU/mL)		−0.000	0.000	.2412	−0.144	1.000	0.999	1.000
9	Intercept	382	−1.040	0.359					
	FEV_1 (L)		−0.152	0.180	.3975	−0.060	0.859	0.604	1.221
10	Intercept	382	−1.065	0.150					
	OCS at V0		−0.792	0.283	**.0052**	−0.213	0.453	0.260	0.789
11	Intercept	382	−1.180	0.139					
	OCS dose V0		−0.034	0.017	**.0435**	−0.216	0.966	0.935	0.999
12	Intercept	382	−1.365	0.174					
	Exacerbations at V0 (n)		0.009	0.029	.7559	0.021	1.009	0.953	1.069
13	Intercept	382	−1.209	0.187					
	Smoker (ex-/smoker = 1)		−0.211	0.253	.4036	−0.058	0.810	0.493	1.329
14	Intercept	382	−1.298	0.129					
	COPD		−0.599	0.632	.3435	−0.079	0.549	0.159	1.897
15	Intercept	380	−1.209	0.174					
	Allergic rhinitis		−0.230	0.252	.3612	−0.064	0.794	0.484	1.302
16	Intercept	254	−1.274	0.197					
	Nasal polyps		0.566	0.288	**.0488**	0.154	1.762	1.003	3.096
17	Intercept	382	−2.251	0.248					
	Biologic at V1		1.503	0.292	**<.0001**	0.415	4.495	2.537	7.965
18	Intercept	382	−1.344	0.265				.	.
	GINA step 5 treatment		0.020	0.301	.9476	0.005	1.020	0.566	1.839
19	Intercept	382	−1.892	0.362					
	ACT points at V0		0.042	0.025	.0896	0.116	1.043	0.994	1.094

COPD, Chronic obstructive pulmonary disease; GINA, Global Initiative for Asthma; *FENO*, fractional exhaled nitric oxide; *ICD-10*, *International Classification of Diseases, Tenth Revision; ppb*, parts per billion.
P values considered significant (<.05) are highlighted in bold.

We demonstrate that most patients treated with biologics showed a good response, whereas only 11.9% were nonresponders after 1 year. Previous real-life studies found similar results (even though the definitions of response were not exactly as used here): Drick at al[15] found 24% nonresponders to anti−IL-5 treatment using a binary classification of response and nonresponse, and Eger et al[12] found 11.9% nonresponders using a ternary classification of super response, partial response, and nonresponse.

So far, few studies have assessed the newly proposed definitions of remission under therapy to patients with severe asthma. A recent retrospective analysis of the randomized controlled trials SIROCCO/CALIMA found a remission rate of 20.6% in the benralizumab group and 13.4% in the placebo group after 12 months of treatment when using a pure clinical remission (R) definition (6-item Asthma Control Questionnaire [ACQ-6] score $\leq$0.75 was used as a criterion for good asthma control) and remission rates of 14.5% and 7.7%, respectively, when including an increase of greater than or equal to 100 mL in FEV_1 as an additional criterion (RL). In our real-life analysis (using ACT score $\geq$20 as a criterion for good asthma control), we found a clinical remission rate in patients newly treated with biologics of 37.6%, and of 32.1% when using the additional criterion of FEV_1 improvement. We used the ACT score instead of the

TABLE IV. Multiple logistic regression analysis of remission RL and baseline parameters in the total cohort (group A + group B)

							95% CI (Wald) for odds ratio	
Item	**N**	**Estimate**	**SE**	***P* value**	**Standardized estimate**	**Odds ratio**	**Lower limit**	**Upper limit**
Intercept	213	−3.7777	1.0033	.0002				
OCS V0		−0.7357	0.3516	**.0364**	−0.1959	0.479	0.241	0.954
Nasal polyps		0.2703	0.3430	.4307	0.0741	1.310	0.669	2.567
Age at asthma diagnosis		0.5658	0.4598	.2185	0.1287	1.761	0.715	4.336
Biologic at V1		0.8684	0.3757	**.0208**	0.2262	2.383	1.141	4.976
Eosinophil threshold		0.5551	0.2277	**.0148**	0.2533	1.742	1.115	2.722

Parameters with *P* values considered significant (<.05) are highlighted in bold.

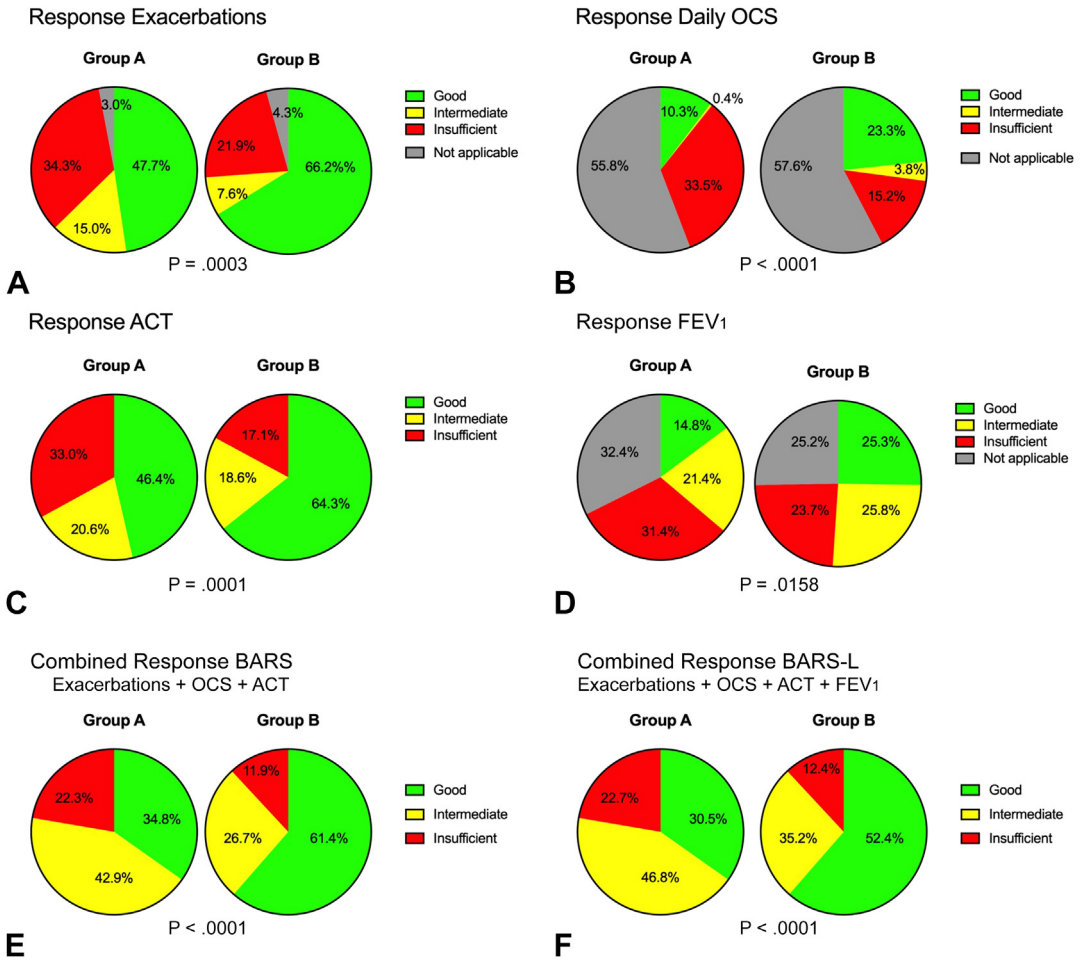


FIGURE 3. Rates of response at 1-year visit (V1) in patients with severe asthma treated without biologics (group A) or with biologic (group B) graded into good, intermediate, and insufficient response according to BARS. (**A**) Criterion exacerbations. (**B**) Criterion daily OCS therapy. (**C**) Criterion ACT. (**D**) Criterion FEV_1. (**E**) Rates of response of combined score using 3 criteria (BARS) and (**F**) using 4 criteria (BARS-L). *P* value: group A vs B by χ^2 test. A parameter is not applicable for response assessment if no further improvement from baseline was possible, eg, when a patient did not use OCS at baseline. For calculation of BARS, this parameter is disregarded.

ACQ-6 score for assessment of symptoms for 2 reasons: it is covering a longer time period (4 weeks instead of 1), and it is widely used in clinical practice. The higher rates of clinical remission in our analysis could in part be because the criterion of ACQ-6 score less than or equal to 0.75 for asthma control might be more strict than the criterion of ACT score greater than or equal to 20.

Of note, clinical remission after 1 year was not only found in patients treated with biologics (37.6%) but also found in patients not treated with biologics (17.2%). Interestingly, in the placebo group of the benralizumab randomized controlled trials, 49.8% of the patients had no exacerbations over 12 months and 48.9% displayed an FEV_1 improvement of 100 mL or more: these effects might be attributed to improved care and inhaled treatment

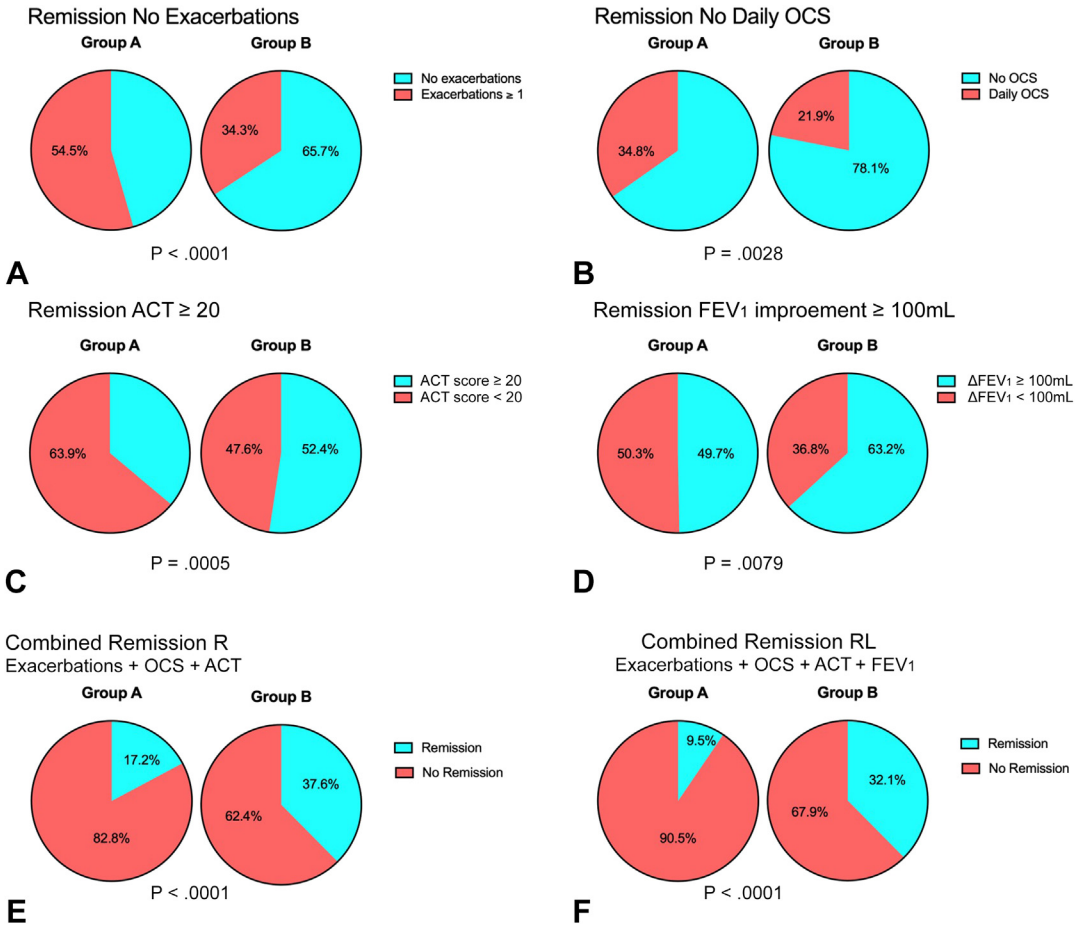


FIGURE 4. Rates of remission at 1-year visit (V1) in patients with severe asthma treated without biologics (group A) or with biologic (group B). (**A**) Criterion: No exacerbation. (**B**) Criterion: No daily OCS. (**C**) Criterion: ACT score 20 or more. (**D**) Criterion: deltaFEV$_1$ 100 mL or more. (**E**) Rates of remission combined out of 3 criteria (R) or (**F**) out of 4 criteria including FEV$_1$ (RL). *P* value: group A vs B by χ^2 test. A parameter is not applicable for response assessment if no further improvement from baseline was possible, eg, when a patient did not use OCS at baseline. For calculation of BARS, this parameter is disregarded.

under study conditions. In our study, improvements in patients not treated with biologics may be due to being managed at a severe asthma center, including optimization of inhaled treatments, management of comorbidities, and closer follow-up with subsequently improved treatment adherence. Similarly, in the UK severe asthma cohort, benefits of management at severe asthma centers were noted even without use of biologics.[25]

Our comparator group treated without biologics should not be mistaken for an equivalent of a placebo group. Notably, these patients (although fulfilling the definition of severe asthma) had less severe disease at baseline, especially less exacerbations and symptoms. The reasons why these patients did not receive a biologic during the study period were not recorded in the registry; however, less severe disease might have played a role. At least half the patients in group A had existing options for escalation of inhaled treatment (eg, addition of a long-acting muscarinergic agonist or further increase in the ICS dose). In addition, patients who had only 1 or no exacerbation in the past year might have been regarded as ineligible for biologics even if their symptoms are uncontrolled on high-dose dual or triple inhaled therapy. In addition, lower type 2 inflammation biomarkers might have been another reason for not using a biologic in group A even though still more than 60% of group A fulfilled common biomarker thresholds of BEC greater than or equal to 150/μL and/or fractional exhaled nitric oxide greater than or equal to 25 ppb.

However, despite less severe baseline characteristics, outcomes after 1 year were worse and remission rates substantially lower in patients treated without a biologic (group A) than in patients treated with a biologic. On the one hand, these real-world findings support the recommendation to use biologics in patients with severe asthma, especially those with frequent exacerbations and/or continuous OCS use.[26] On the other hand, the data raise the question whether future use of biologics should remain limited to patients with frequent exacerbations and/or continuous OCS use, or whether patients "only" having uncontrolled symptoms under high-dose inhaled therapies might also benefit from these treatments. Importantly, high-dose ICSs also have systemic (side) effects,[27,28] which might be avoided if biologics would be given to patients with less severe disease. Taken together, our results suggest that careful evaluation and management of patients with severe asthma at specialist centers may already lead to meaningful improvements (effects in group A) and that biologic treatment is a strong additional factor (effects in group B).

Multivariate regression analyses confirmed that the use of biologics had the strongest influence on the occurrence of asthma remission. However, biomarker levels fractional exhaled nitric oxide and BEC were also higher in group B than in group A and these are known predictors of response to biologic therapies, especially anti−IL-5/R and anti−IL-4R. Physician's knowledge of more systemic type 2 inflammation disease and predictors of response may have influenced the decision to start a biologic and this influence cannot be measured or controlled for our real-life study. Of note, in these regression analyses all biologics were analyzed together, because the number of patients especially in the anti-IgE group (n = 33) was too small for meaningful statistical analyses of each biologic individually. Because the anti−IL-5/R group had the largest number of patients, the associations found here are mainly driven by this group and may not sufficiently reflect predictors of response in the anti-IgE group.

Recently, different proposals to quantify response to biologics in severe asthma have been made. Some were developed for research purposes containing measures that apply only to certain biologics.[15] Here, we used the BARS, which was developed as a simple tool to assess the response to biologics in clinical practice to help clinicians decide whether a biologic should be continued, switched, or stopped.[19] Other scores have been proposed such as the FEOS (FEV1, exacerbations, oral steroids, symptoms): this score uses the parameters FEV_1, exacerbations, OCS use, and symptoms but divides each criterion into 4 or 5 response classes and applies a weighted system to each criterion, resulting in a finer response classification but also need for using a calculator.[16] An even more comprehensive initiative to define response to biologics in asthma is under way within the "3TR" consortium, a pan-European initiative including not only pediatric and adult clinicians from different countries but also perspectives from patients, health care regulators, and pharmaceutical representatives.[29] The consented core outcome measures include FEV_1, annual frequency of severe exacerbations, maintenance OCS use, symptom scores (ACT, ACQ-6), and/or quality of life (Asthma Quality of Life Questionnaire).[30] However, the exact definitions and thresholds of treatment response and remission are still in dispute. In our BARS,[19] pulmonary function parameters were optional, because there might be other reasons for impaired lung function (such as early-life events or comorbidities) and because pulmonary function responses may vary depending on duration of disease. Of note, BARS proposes to take into account not only FEV_1 but also residual volume and airway resistance, because larger responses may be observed in these parameters.[31] However, for reasons of comprehensibility and comparability, we used only FEV_1 in the current analysis. It needs to be noted that thresholds for FEV_1 improvements under treatment are currently debated, because there are no established minimally clinically important differences. Recently, the use of the FEV_1 improvement of more than or equal to 100 mL as remission criterion was criticized as too low.[32]

One may ask whether treatment response and the occurrence of remission are indeed different, because they use the same criteria here, only with different thresholds. In our view, the 2 concepts are complementary. Response focuses on the amount of improvement relative to baseline, so that patients with most severe disease are classified as good responders even if they are still symptomatic. Remission on treatment is the higher goal, with absolute thresholds valid irrespective of asthma severity, but may not be achievable in all patients with severe asthma. Finally, even though the introduction of the term "remission on treatment" is new, Global Initiative for Asthma has introduced concepts that paved the way to the concept of remission: as-needed ICS/fast-acting beta therapy is recommended in all treatment steps to prevent exacerbations and the broader definition of asthma control has not only included symptoms, but extends to preventing exacerbations and limiting treatment-related side effects.[33]

Limitations

Limitations of the study are mainly related to the retrospective design of the study and the real-life nature of the cohort. In addition, because of the definition of remission that observes outcome in a 12-month period, we included only those patients who had data for the 4 outcome parameters in the whole observation period: this led to a smaller study cohort compared with the total baseline GAN cohort. Furthermore, it cannot be excluded that loss-to-follow-up or incomplete data might have occurred more frequently in patients responding less well to therapy. Finally, because of limited numbers for individual biologics, we did not differentiate between the different biologics for the main analyses and a comparison of biologics was also not the aim of the study. Still, patients treated with different biologics represent different phenotypes of severe asthma, for example, early-onset allergic phenotype (candidates for omalizumab treatment) or adult-onset eosinophilic phenotype (candidates for treatments targeting the IL-5 pathway): these phenotypes might be associated with other differences in baseline characteristics and possibly, consecutive differences in the treatment response.

CONCLUSIONS

Real-world patients with severe asthma treated with biologics have a higher probability of achieving remission than patients not treated with biologics, despite more severe disease at baseline. Measuring treatment response and the occurrence of asthma remission are complementary in guiding treatment decisions and advancing goals in severe asthma.

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TABLE E1. Univariate logistic regression analysis of remission RL and baseline parameters in group A (without biologics)

No.	Item	N	Estimate	SE	*P* value	Standardized estimate	Odds ratio	95% CI (Wald) for odds ratio	
								Lower limit	Upper limit
1	Intercept	173	−1.184	1.139					
	Age (y)		−0.022	0.022	.3031	−0.152	0.978	0.937	1.020
2	Intercept	189	−2.284	0.316					
	Sex (1 = male, 0 = female)		0.087	0.509	.8642	0.023	1.091	0.402	2.957
3	Intercept	140	−1.955	0.491					
	Duration of asthma bronchiale (y)		−0.029	0.025	.2418	−0.243	0.971	0.925	1.020
4	Intercept	189	−1.831	0.917					
	Age at asthma diagnosis (y)		−0.248	0.528	.6388	−0.062	0.780	0.277	2.197
5	Intercept	189	−2.447	0.347					
	ICD-10: Allergic asthma		0.440	0.497	.3759	0.119	1.552	0.586	4.110
6	Intercept	127	−2.975	0.798					
	Eosinophile threshold		0.445	0.326	.1719	0.221	1.561	0.824	2.956
7	Intercept	82	−1.929	0.528					
	FENO at presentation day (ppb)		0.004	0.010	.6883	0.066	1.004	0.985	1.023
8	Intercept	80	−1.863	0.368					
	Total IgE (IU/mL) (actual)		0.000	0.000	.8757	0.027	1.000	0.999	1.001
9	Intercept	189	−1.991	0.719					
	FEV_1 (L)		−0.140	0.369	.7038	−0.053	0.869	0.421	1.792
10	Intercept	189	−1.741	0.263					
	OCS V0		−2.563	1.041	**.0138**	−0.693	0.077	0.010	0.593
11	Intercept	189	−1.760	0.262					
	OCS dose V0		−0.379	0.209	.0704	−2.362	0.685	0.455	1.032
12	Intercept	189	−2.165	0.353					
	Exacerbations in the last 12 mo: how often		−0.025	0.075	.7410	−0.049	0.976	0.843	1.130
13	Intercept	189	−1.932	0.338					
	Ex-/Smoker		−0.614	0.499	.2188	−0.167	0.541	0.203	1.440
14	Intercept	189	−2.248	0.255					
	COPD		−0.054	1.079	.9598	−0.007	0.947	0.114	7.855
15	Intercept	187	−1.946	0.309					
	Allergic rhinitis/rhinoconjunctivitis		−0.705	0.523	.1778	−0.195	0.494	0.177	1.378
16	Intercept	96	−1.833	0.381					
	Nasal polyps		0.159	0.586	.7865	0.043	1.172	0.372	3.693
71	Intercept	189	−3.908	0.821					
	ACT points V0		0.112	0.049	**.0220**	0.321	1.119	1.016	1.232
18	Intercept	189	−2.478	0.301					
	GINA step 4		0.938	0.541	.0831	0.199	2.554	0.884	7.374
19	Intercept	189	−1.431	0.336					
	GINA step 5		−1.452	0.513	**.0047**	−0.368	0.234	0.086	0.640

COPD, Chronic obstructive pulmonary disease; *GINA*, Global Initiative for Asthma; *FENO*, fractional exhaled nitric oxide; *ICD-10*, *International Classification of Diseases, Tenth Revision*; *ppb*, parts per billion.
P values considered significant (<.05) are highlighted in bold.

TABLE E2. Multiple logistic regression analysis of remission RL and baseline parameters in group A (without biologics)*

Item	N	Estimate	SE	*P* value	Standardized estimate	Odds ratio	95% CI (Wald) for odds ratio	
							Lower limit	Upper limit
Intercept	189	−3.2760	0.8465					
ACT points V0		0.1027	0.0506	**.0424**	0.2937	1.108	1.004	1.224
OCS V0		−2.4863	1.0439	**.0172**	−0.6724	0.083	0.011	0.644

GINA, Global Initiative for Asthma.

P values considered significant (<.05) are highlighted in bold.

*Significant parameters from univariate analysis were included except for GINA step 5 treatment because this was per definition correlated with OCS.