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Clinical Response and Remission in Patients With Severe Asthma Treated With Biologic Therapies

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BACKGROUND: The development of novel targeted biologic therapies for severe asthma has provided an opportunity to consider remission as a new treatment goal.

RESEARCH QUESTION: How many patients with severe asthma treated with biologic therapy achieve clinical remission, and what predicts response to treatment?

STUDY DESIGN AND METHODS: The Danish Severe Asthma Register is a nationwide cohort including all adult patients receiving biologic therapy for severe asthma in Denmark. This observational cohort study defined "clinical response" to treatment following 12 months as a $\geq$ 50% reduction in exacerbations and/or a $\geq$ 50% reduction in maintenance oral corticosteroid dose, if required. "Clinical remission" was defined by cessation of exacerbations and maintenance oral corticosteroids, as well as a normalization of lung function ($FEV_1 > 80\%$) and a six-question Asthma Control Questionnaire score $\leq$ 1.5 following 12 months of treatment.

RESULTS: Following 12 months of treatment, 104 (21%) of 501 biologic-naive patients had no response to treatment, and 397 (79%) had a clinical response. Among the latter, 97 (24%) fulfilled the study criteria of clinical remission, corresponding to 19% of the entire population. Remission was predicted by shorter duration of disease and lower BMI in the entire population of patients treated with biologic therapy.

INTERPRETATION: Clinical response was achieved in most adult patients initiating biologic therapy, and clinical remission was observed in 19% of the patients following 12 months of treatment. Further studies are required to assess the long-term outcome of achieving clinical remission with biologic therapy.

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KEY WORDS: biologics; epidemiology; remission; severe asthma

ABBREVIATIONS: ACQ-6 = six-question Asthma Control Questionnaire; DSAR = Danish Severe Asthma Register; mOCS = maintenance oral corticosteroid; OCS = oral corticosteroids

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Take-home Points

Study Question: How many patients with severe asthma treated with biologic therapy achieve clinical remission, and what predicts response to treatment?
Results: This study highlights that almost one in five patients with severe asthma achieve remission following treatment with biologic therapy. Remission was predicted by shorter disease duration at time of treatment initiation and lower BMI.
Interpretation: Clinical remission is an achievable treatment goal in adult patients with severe asthma. Larger prospective studies are needed to describe the impact of remission on treatment on longer-term clinical outcomes.

Severe asthma is a highly burdensome condition, affecting approximately 5% to 10% of patients with asthma whose disease remains uncontrolled despite high-dose controller therapy and in whom other causes, including lack of adherence, inadequate inhaler technique, and influence of untreated comorbidities, have been ruled out.[1-4] Severe asthma is associated with high morbidity, loss of quality of life, and iatrogenic side effects to treatment, most notably from oral corticosteroids (OCS) prescribed either intermittently to treat exacerbations or as maintenance therapy (maintenance OCS [mOCS]).[5,6]

Previously, asthma treatment has been focused on achieving disease control.[7,8] However, with the development of novel biologic therapies targeting the underlying inflammatory mechanisms, it is natural to consider remission as an achievable treatment target in severe asthma. A similar shift in disease management has been observed in rheumatology. Disease-modifying antirheumatic drugs and targeted biologic therapies have transformed the view on the course of rheumatoid arthritis from a chronic disease to a potentially curable condition, and remission on treatment has been associated with minimal or no clinically detectable disease activity persisting in some patients even after tapering or discontinuing the biologic therapy.[9]

Remission as a treatment outcome is clinically important at two levels. First, patients who achieve complete control of their asthma may have a better long-term prognosis in terms of a reduced risk of excessive lung function decline and future exacerbations. Second, patients achieving clinical remission may also have a better chance of tapering biologic therapy.[10] Hence, understanding the likelihood and predictors of remission is clinically important and a key step toward describing the longer term beneficial implications of achieving short-term remission on a biologic treatment.

There is currently no clear consensus as to what constitutes clinical response or remission in severe asthma, but a definition has been proposed by Menzies-Gow et al.[8] They include definitions of remission on and off treatment, using varying combinations and cutoffs of absence of symptoms, no OCS use for asthma, stabilization of lung function, and agreement by health care professional and patient about remission assessed over a period of 12 months. This definition of remission may be regarded as a more clinically relevant outcome than previous definitions of super-response,[11] as it describes whether the patient achieves complete control following treatment rather than the magnitude of response, which is dependent on the baseline level of control.

The aim of the current study was to describe the real-life effectiveness of biologic therapy in severe asthma, to evaluate the proportion of patients who achieve a clinical response and clinical remission, and to identify predictors of nonresponse and remission.

Study Design and Methods

Study Population and Design

Patients were included from the Danish Severe Asthma Register (DSAR), a nationwide cohort of all patients treated with a biologic for severe asthma in Denmark.[12] Patient information in DSAR is collected prospectively and follows a clinical protocol with a baseline visit when biologic treatment is commenced, following 4 and 12 months of treatment, and then annually. DSAR is approved by Videnscenter for Dataanmeldelser in the Capital Region (VD-2018-31), and all patients provide written consent for their data to be used for research.

For the current analysis, biologic-naive patients commencing biologic therapy between January 1, 2016, and December 31, 2021, were included. All but two patients were aged ≥ 18 years at time of treatment start (the remaining two patients were 16 and 17 years of age, respectively). Indication criteria for all biologic therapies in Denmark are described in e-Table 1. As illustrated, in addition to fulfilling the criteria for biologic therapy (high-dose inhaled corticosteroids plus a second controller), adherence to treatment, and a complete systematic assessment, all patients must have had ≥ 2 exacerbations in the previous 12 months or use mOCS at least 50% of the time in the previous 12 months to qualify for biologic therapy. Patients were included who fulfilled these criteria and for

whom complete data were available. A flowchart of the study population is presented in e-Figure 1.

Study Definitions

The current study assessed two levels of response to treatment after 12 months: clinical response and clinical remission. To define clinical response, we applied a definition reflecting the clinical response that would be perceived as clinically relevant. Hence, in the clinical setting, a clinically relevant response should include an effect on the criteria that set the indication: either exacerbations and/or mOCS use. Clinical response was defined as: (1) a reduction of at least 50% in the annualized exacerbation rate if the indication was based on $\geq$ 2 exacerbations in the 12 months prior to treatment, and (2) a reduction of at least 50% in the OCS dose from baseline if the indication was based on the need for mOCS. If a patient fulfilled both criteria, a reduction in exacerbations of at least 50%, while maintaining OCS use, was also considered a clinically relevant response, whereas a reduction in OCS dose without a reduction in exacerbations was not, as this would likely indicate undertreatment with OCS to some extent. Nonresponse was defined as patients not fulfilling the criteria for clinical response, as well as discontinuation or switching treatment prior to 12 months. For clinical remission, the definition proposed by Menzies-Gow et al[8] was applied: clinical remission on treatment following 12 months of treatment was defined as a complete absence of exacerbations and need for mOCS and well-controlled symptoms defined as a score on the six-question Asthma Control Questionnaire (ACQ-6) of $\leq$ 1.5 after 12 months of treatment. Optimization and stabilization of lung function were interpreted as a normalization of lung function (FEV_1 > 80% of predicted value).

Analyses

Continuous variables are described by mean $\pm$ SD and median (25th percentile-75th percentile); categorical variables are described as number (%). The effectiveness of biologic therapy was assessed in all biologic therapies combined by describing the change in ACQ-6, FEV_1 percent predicted value, exacerbations, and mOCS use in the overall study population using paired *t* tests or signed-rank test for continuous variables, where appropriate, and by McNemar test for categorical variables. Furthermore, we calculated the proportion of patients with no response vs a clinical response to biologic therapy following 12 months of treatment and the proportion of patients going into clinical remission in the full study population and in the three drug classes (anti-IgE, anti-IL-5/IL-5 receptor [IL-5R], and anti-IL-4 receptor alpha subunit [IL-4Rα]).

Baseline characteristics of patients were compared according to response to treatment using χ^2 tests for categorial variables and *t* tests and *U* tests for parametric and nonparametric variables, respectively. This was done in the entire population and in the individual drug classes.

The association between baseline characteristics that in univariate analyses were associated with remission with $P < .10$ were furthermore included in a multivariate logistic regression model to examine their independent impact on the odds of achieving remission. Variables that were part of the remission definition (exacerbations, mOCS, ACQ-6, and FEV_1 percent predicted) were not included in this model, neither were the comorbidities associated with remission to avoid including too many categorical variables that would lead to a regression model that would not converge. Finally, due to collinearity, duration of disease and asthma onset could not both be included in the same model; we chose to keep duration of disease in the final model.

All *P* values were two-sided and considered significant at $\alpha < 0.05$. If there were less than five observations in a cell, *P* values were based on the Fisher exact test. No *P* values were presented if the Fisher exact test did not converge. Analyses were conducted by using SAS Enterprise guide (SAS Institute, Inc.).

Results

Of the 775 biologic-naive patients identified in the DSAR, 501 fulfilled the criteria for the current study (e-Fig 1). Baseline characteristics of the population are summarized in Table 1, and the indications for commencing biologic therapy in the entire study population are illustrated in e-Figure 2.

The overall effectiveness of biologic therapy is shown in Figure 1. Following 4 months of treatment, the mean ACQ-6 score had decreased from 2.52 $\pm$ 1.22 to 1.54 $\pm$ 1.15; following 12 months, it had decreased to 1.47 $\pm$ 1.19, compared with baseline, thus meeting the minimal clinically important difference of a change of at least 0.5. An improvement was observed in FEV_1 from 2.24 $\pm$ 0.90 L to 2.49 $\pm$ 0.92 L after 4 months and to 2.42 $\pm$ 0.90 L after 12 months, which was statistically significant; the findings reached a minimal clinically important difference of 0.2 L after 4 months but not after 12 months. At the 12-month follow-up, 325 patients (68%) had not experienced any OCS-related exacerbations since commencing biologic treatment. At baseline, 211 (42%) patients were taking mOCS; after 12 months of follow-up, 114 (25%) patients were using mOCS.

After 12 months of treatment, 397 (79%) patients fulfilled the study criteria for a clinical response in the indication that set the treatment, whereas 104 (21%) had no response to treatment (Fig 2). Among the 397 clinical responders, 97 patients (24% of those with a clinical response, 19% of the total study population) had achieved clinical remission. For the three individual drug classes, the proportion of clinical response varied from 72% in anti-IgE, 78% in anti-IL-5/IL-5R, and 92% in anti-IL-4Rα, whereas the proportions of patients achieving remission in these three groups were 6%, 19%, and 30%, respectively (Fig 3).

In the overall population, we found few baseline predictors of having a clinical response to biologic therapy compared with no response (Fig 2, Table 2). Nonresponders were more likely to use mOCS at baseline compared with clinical responders and to have fewer exacerbations. They were also less likely to have blood eosinophils $\geq$ 0.3 cells $\times$ 10^9/L and to have eosinophilic pneumonia. Patients achieving remission were more likely to be male, to have a lower BMI, to be older at asthma onset, to not use mOCS, to have a lower ACQ-6 score, to have higher FEV_1 and FEV_1 percent

TABLE 1] Baseline Characteristics of Biologic-Naive Patients Commencing Biologic Therapy in the Danish Severe Asthma Register

Baseline Variable	Study Population (N = 501)
Demographic variables	
Age, y	56 ± 14
Female	254 (51)
BMI, kg/m^2	28 ± 6
Duration of disease, y	22 ± 18
Duration of disease ≥ 10 y	244 (62)
Age at asthma onset, y	34 ± 21
Onset during childhood (age ≤ 18 y)	125 (31)
Late onset (age ≥ 40 y)	179 (45)
Smoking status	
Never smoked	262 (53)
Previously smoked	227 (46)
Currently smokes	6 (1)
Pack-y in previously smoked and currently smokes	13 (4-23)
Symptom control	
ACQ-6 score	2.52 ± 1.22
ACQ-6 score ≤ 1.5	91 (25)
Exacerbations past 12 mo	3.00 (2.00-5.00)
Medication use	
Budesonide equivalent dose, μg	1,600 (800-1,600)
mOCS	211 (42)
mOCS dose, mg	10.00 (5.00-12.50)
ICS	221 (44)
ICS/LABA	357 (71)
ICS/LABA/LAMA	27 (5)
LAMA	178 (36)
LABA/LAMA	30 (6)
SABA	262 (52)
LTRA	217 (43)
Theophylline	23 (5)
Lung function	
FEV_1, L	2.24 ± 0.85
FEV_1, percent predicted	69 ± 21
FEV_1/FVC	0.66 ± 0.15
Allergy	
Positive SPT and/or positive specific IgE	183 (50)
Positive SPT	57 (49)
Positive specific IgE	159 (51)
Inflammatory markers	
Blood eosinophils, cells × 10^9/L	0.34 (0.14-0.62)
Blood eosinophils ≥ 0.3 10^9/L (%)	264 (56)
IgE, IU/mL	144 (54-381)
IgE ≥ 150 IU/mL	173 (49)
FENO, ppb	32 (16-64)
FENO ≥ 25 ppb	258 (61)
Comorbidities	
ABPA	18 (4)
Allergic rhinitis	252 (51)
Atopic dermatitis	87 (18)
Aspirin sensitivity	35 (7)
Bronchiectasis	125 (25)
Cardiovascular disease	142 (29)
Chronic rhinosinusitis	294 (60)
COPD	104 (21)
Diabetes	41 (8)
Dysfunctional breathing	40 (8)
EGPA	14 (3)
Eosinophilic pneumonia	18 (4)
GERD	149 (31)
Nasal polyposis	203 (42)
Obesity (BMI ≥ 30 kg/m^2)	141 (29)
OSA syndrome	57 (12)
Psychiatric disease	66 (13)
Vocal cord dysfunction	9 (2)

Data are presented as mean ± SD, No. (%), or median (25th percentile-75th percentile). ABPA = allergic bronchopulmonary aspergillosis; ACQ-6 = six-question Asthma Control Questionnaire; EGPA = eosinophilic granulomatosis with polyangiitis; FENO = fractional exhaled nitric oxide; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; mOCS = maintenance oral corticosteroid; SABA = short-acting beta-agonist; SPT = skin prick test.

predicted, and to have higher median blood eosinophil count (Fig 2, Table 3). There were also less likely to have COPD, dysfunctional breathing, and nasal polyposis. In a multivariate model, the strongest predictors of remission were BMI (OR for 1 unit increase, 0.91; 95% CI, 0.86-0.97) and duration of disease (OR for 1 year increase, 0.98; 95% CI, 0.97-0.99) (Table 4). Doubling concentrations of blood eosinophil count and fractional exhaled nitric oxide yielded ORs of 1.18 (95% CI, 0.98-1.42) and 1.02 (95% CI, 0.81-1.27),

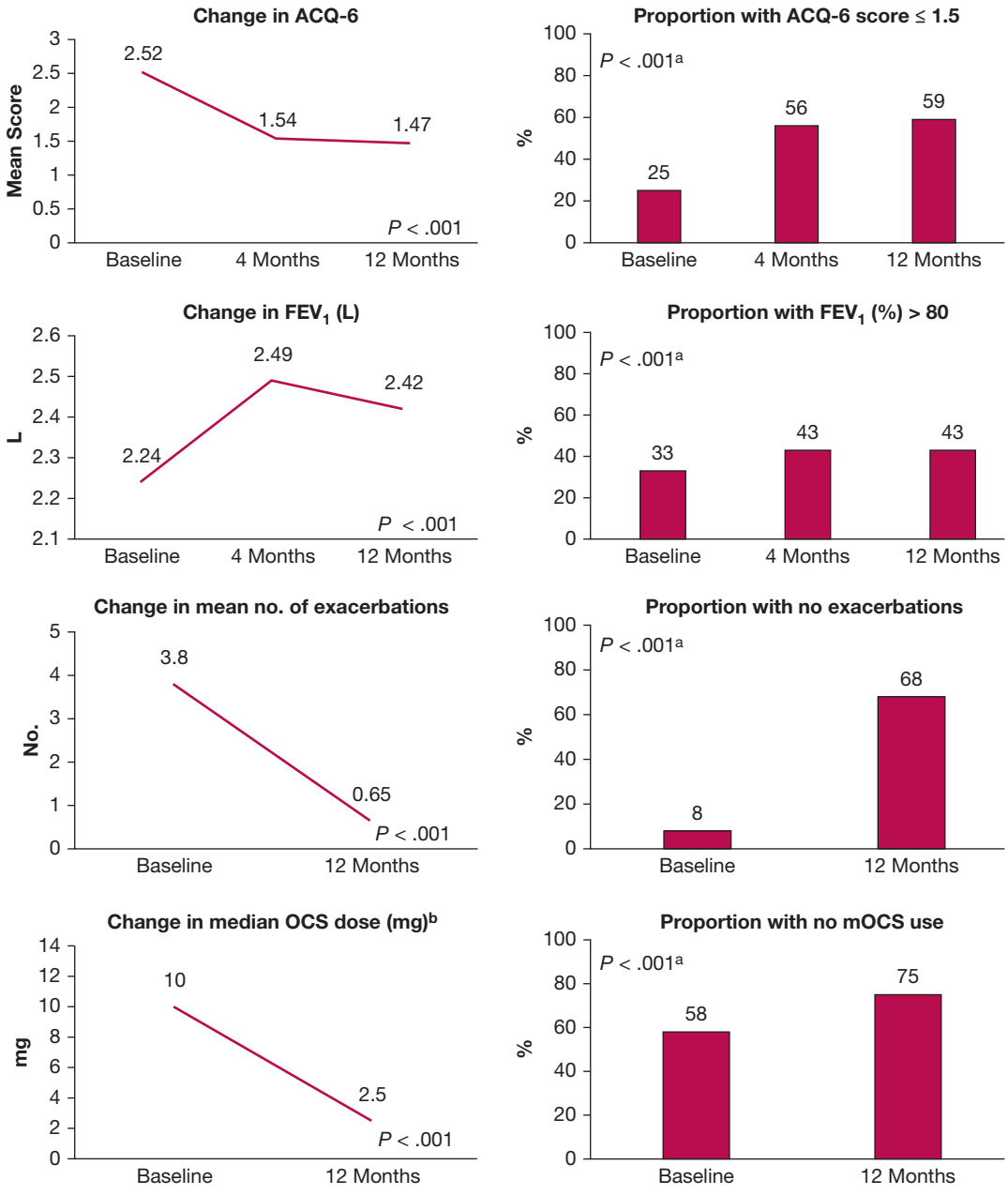
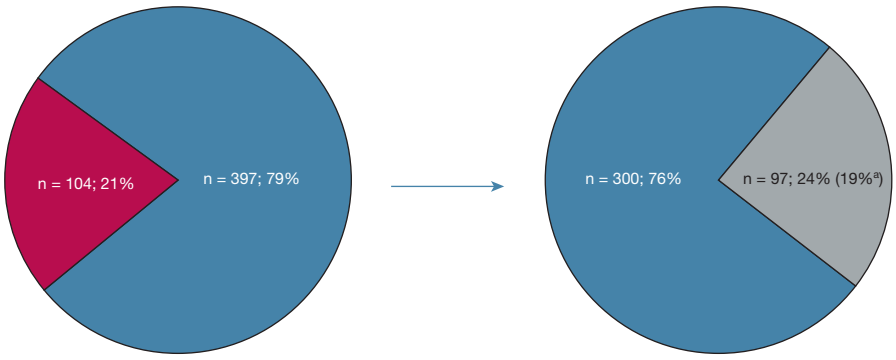


Figure 1 – *Effectiveness of biologic therapy on clinical outcomes in the Danish Severe Asthma Register (N = 501).* [a]P *values from paired* t *test or signed rank test for continuous variable and McNemar test for categorical variables comparing the change between baseline and 12 months.* [b]*Median OCS dose at 12 months presented for patients who were using at baseline. Those not using at 12 months therefore contribute with a value of 0 mg. mOCS = maintenance oral corticosteroid; OCS = oral corticosteroid.*

respectively, and male sex was associated with an OR of 1.57 (95% CI, 0.88-2.83), compared with female sex.

Regarding the individual drug classes, biomarkers that predicted remission are illustrated in Figure 3, and all predictors of response are presented in e-Tables 2 to 4. Remission in patients treated with anti-IL-5/IL-5R was predicted by higher baseline blood eosinophils and higher total IgE, whereas remission in patients treated with anti-IL-4Rα was predicted by higher fractional exhaled nitric oxide levels.

The temporal response to biologic therapy in patients with a clinical response and remission is illustrated in Figure 4. In patients obtaining a clinical response to treatment, 17% had a baseline ACQ-6 score ≤ 1.5; this number improved to 50% following 4 months and slightly declined to 48% following 12 months. In patients



	No response	Clinical response[b]	P
mOCS	n = 65 (63%)	n = 146 (37%)	< .001
Exacerbations	3 (1, 4)	3 (2, 5)	< .001
Blood eosinophils ≥ 0.3 (cells × 10^9L)	n = 42 (44%)	n = 222 (59%)	.01
Eosinophilic pneumonia	n = 8 (9%)	n = 10 (3%)	.01

	Clinical response[c]	Clinical remission	P
Female	n = 162 (54%)	n = 37 (38%)	.01
BMI, kg/m^2	28 ± (6)	26 ± (4)	.01
Disease duration, y	23 ± (19)	18 ± (17)	.02
Age at asthma onset, y	33 ± (21)	38 ± (21)	.04
Blood eosinophils (cells × 10^9L)	0.32 (0.13, 0.58)	0.50 (0.25, 0.75)	.01
COPD	n = 70 (24%)	n = 9 (9%)	.003
Dysfunctional breathing	n = 30 (10%)	n = 2 (2%)	.01
Nasal polyposis	n = 114 (38%)	n = 52 (54%)	.01

[a]Proportion in the entire population
[b]Clinical response, including remission
[c]Clinical response, excluding remission

Figure 2 – *Response pattern and predictors of response following 12 months of treatment with biologic therapy in biologic-naive patients in the Danish Severe Asthma Register (N = 501). [a]Proportion in the entire population. [b]Clinical response, including remission. [c]Clinical response, excluding remission. mOCS = maintenance oral corticosteroid.*

achieving remission, the proportion with ACQ-6 score ≤ 1.5 went from 47% at baseline to 89% after 4 months. For FEV_1 percent predicted, the proportion of patients with FEV_1 > 80% in patients obtaining a clinical response was 25% at baseline, 29% after 4 months, and 28% after 12 months. In patients achieving remission, the proportion with FEV_1 > 80% improved from 65% at baseline to 92% after 4 months. After 12 months of treatment, 65% of patients obtaining a clinical response had not had any exacerbations, and 75% of patients were free of mOCS use.

Discussion

In this nationwide DSAR cohort of all patients treated with a biologic in Denmark, we found that most patients (79%) obtained a clinically relevant response in the outcomes that set the indication for biologic therapy following 12 months of treatment. Furthermore, approximately one-fifth of all patients achieved clinical remission on treatment with an elimination of exacerbations, no use of mOCS, an ACQ-6 score ≤ 1.5, and a normalization of lung function (> 80% of predicted value). Together, our findings show a beneficial effect in the majority of patients with severe asthma, who fulfill criteria for biologics and further indicate that achieving remission on treatment is, in fact, a realistic goal in a proportion of patients.

The current results are in line with two post hoc analyses of studies with dupilumab[13] and benralizumab[14] that reported remission proportions of 15% to 20% using definitions of remission similar to ours. A recently published study based on real-life data from Germany identified 32% of patients as having achieved remission following 1 year of treatment, with 14%, 38%, and 23% achieving remission in patients treated with anti-IgE, anti-IL5/IL-5R, and anti-IL4Rα, respectively.[15] The definition of remission was, however, different from the current study on two parameters in that it was based on an Asthma Control Test score > 20 and an improvement in FEV_1 of > 100 mL, which could explain the higher rate of remission observed in their study compared with the current one. Another real-life study, by Eger al,[16] identified 14% of patients as having obtained a super-response to anti-IL-5/IL-5R treatment using a composite measure of no use of mOCS, no OCS bursts in the past 3 months, ACQ-6 score < 1.5, FEV_1 ≥ 80%, and fractional exhaled nitric oxide < 50 ppb, as well as complete control of comorbidities to define super-response. Moreover, they identified similar predictors of super-response as in our study that were indicative of an adult patient with a relatively short duration of late-onset eosinophilic asthma having the most benefit from treatment. We additionally observed that a lower BMI increased the chance of achieving

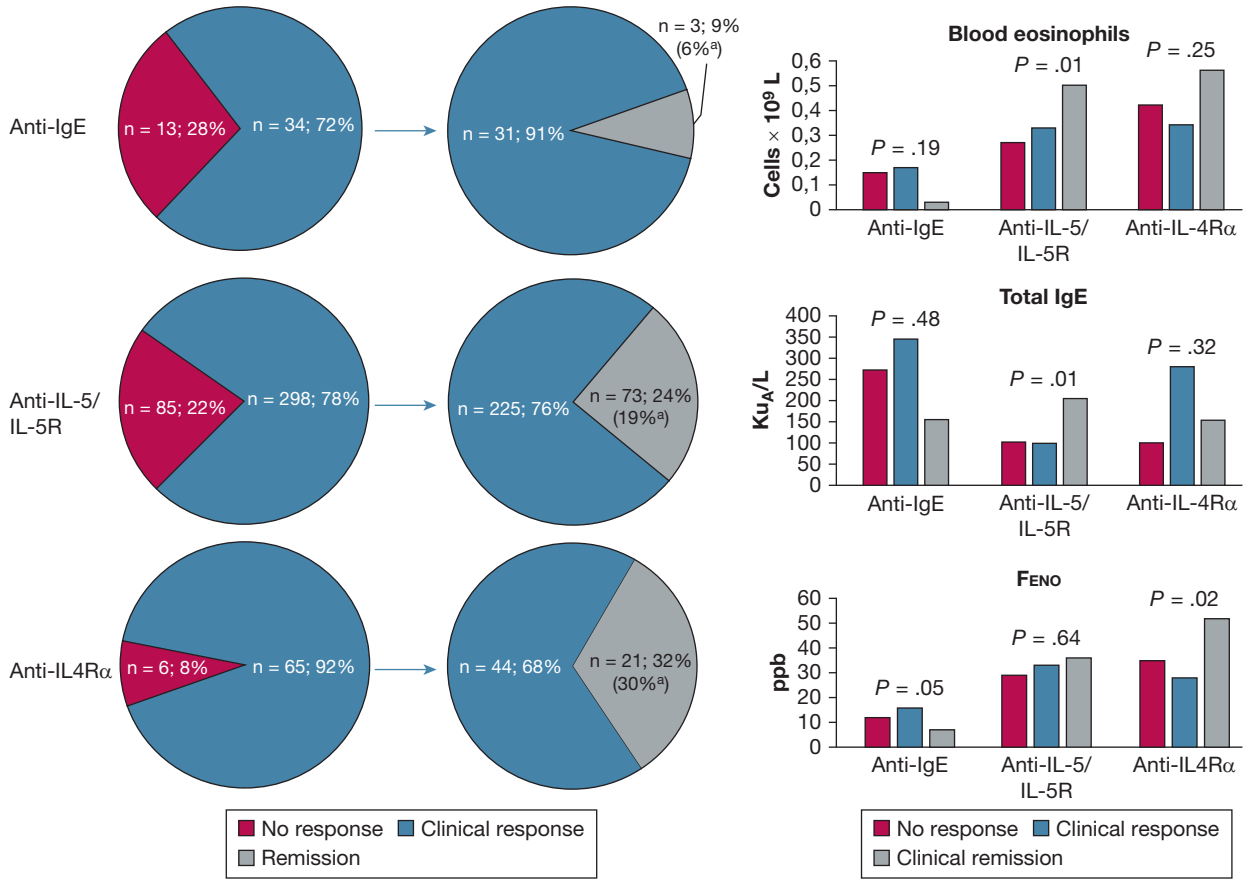


Figure 3 – *Response pattern following 12 months of treatment with biologic therapy and baseline biomarkers predicting remission in each drug class compared with patients with a clinical response.* [a]*Proportion in the entire population.* FENO = *fractional exhaled nitric oxide.*

clinical remission, which corresponds with the fact that obesity as an unmanaged comorbidity negatively affects asthma control and may be associated with reduced steroid responsiveness.[17]

Regarding biomarkers, previous studies have indicated that patients with severe asthma with a higher load of type 2 biomarkers are those who benefit the most from biologic therapy.[15,18,19] We observed a positive association between blood eosinophil count at baseline and remission and in the analyses of the individual drug classes. Furthermore, total IgE predicted remission in anti-IL-5/IL-5R whereas fractional exhaled nitric oxide level predicted remission in anti-IL-4Rα. However, in the multivariate analysis, blood eosinophil count did not remain as an independent predictor in the full data set of all drug classes combined. Preferably, multivariate analyses should have been performed in the individual drug classes, but we did not include enough patients treated with anti-IgE and anti-IL-4Rα to conduct a meaningful statistical analysis. Using type 2 biomarkers to identify patients representing phenotypes driven specifically by IL-5 and IL-4/IL-13, respectively, is important, as our results indicate that these groups of patients will benefit in particular from interventions that target these cytokines. This topic warrants further investigation and should be addressed in larger cohorts or in analyses of pooled data from multiple registries.

In the current study, remission was achieved by 30% of patients treated with anti-IL-4Rα, by 19% of patients treated with anti-IL-5/IL-5R, and by 6% of patients treated with anti-IgE. The low remission proportion among patients in anti-IgE treatment may be explained by the fact that IgE is a relatively downstream mediator of inflammation and therefore, most likely, is the main driver of disease in comparatively few patients. The low remission proportion for anti-IgE could also be explained by a time bias resulting from the fact that anti-IgE was the only biologic drug available for a long time, and some patients who might have been more suited for an anti-IL-5/IL-5R or anti-IL-4Rα treatment may have been prescribed anti-IgE. We did, however, try to eliminate this effect by excluding patients commencing treatment prior to 2016 when only

TABLE 2] Baseline Characteristics Comparing No Response to Clinical Response Following 12 Months of Treatment in All Patients Treated With Biologic Therapies

Baseline Variable	No Response (n = 104)	Clinical Response (Including Patients With Clinical Remission) (n = 397)	*P* Value
Demographic variables			
Age, y	55 ± 15	56 ± 13	.58
Female	55 (53)	199 (50)	.62
BMI, kg/m^2	29 ± 7	28 ± 5	.05
Duration of disease, y	21 ± 19	22 ± 18	.88
Duration of disease ≥ 10 y	45 (62)	199 (63)	.83
Age at asthma onset, y	35 ± 20	34 ± 21	.71
Onset during childhood (age ≤ 18 y)	26 (33)	100 (30)	.58
Late onset (age ≥ 40 y)	31 (41)	146 (45)	.79
Smoking status			.20
Never smoked	55 (53)	207 (53)	
Previously smoked	45 (44)	182 (46)	
Currently smokes	3 (3)	3 (1)	
Pack-y	10 (2-20)	15 (5-25)	.04
Medication use			
Budesonide equivalent dose, μg	1,600 (600-1,600)	1,600 (800-1,600)	.59
mOCS	65 (63)	146 (37)	< .001
mOCS dose, mg	10.00 (5.00-10.00)	10.00 (5.00-12.50)	.26
Biologic class			.02
Anti-IgE	13 (13)	34 (9)	
Anti-IL-5/IL-5R	85 (82)	298 (75)	
Anti-IL-4Rα	6 (6)	65 (16)	
Symptom control			
ACQ-6 score	2.59 ± 1.21	2.50 ± 1.22	.59
ACQ-6 score ≤ 1.5	16 (24)	75 (25)	.86
Exacerbations in the past 12 mo	2.90 ± 2.85	4.01 ± 2.82	< .001
Exacerbations in the past 12 mo	3.00 (1.00-4.00)	3.00 (2.00-5.00)	< .001
Lung function			
FEV_1, L	2.15 ± 0.77	2.27 ± 0.87	.21
FEV_1, percent predicted	67 ± 19	70 ± 22	.18
FEV_1/FVC	0.67 ± 0.14	0.66 ± 0.15	.58
Inflammatory markers			
Blood eosinophils, cells × 10^9/L	0.25 (0.13-0.56)	0.39 (0.15-0.64)	.14
Blood eosinophils ≥ 0.3 10^9/L	42 (44)	222 (59)	.01
IgE, IU/mL	116 (54-343)	147 (55-384)	.36
IgE ≥ 150 IU/mL	30 (46)	143 (50)	.61
F_{ENO}, ppb	28 (13-59)	32 (17-65)	.41
F_{ENO} ≥ 25 ppb	46 (55)	212 (62)	.27
Comorbidities			
ABPA	6 (6)	12 (3)	.16
Allergic rhinitis	46 (46)	206 (52)	.25
Atopic dermatitis	18 (18)	69 (18)	.94
Aspirin sensitivity	4 (4)	31 (8)	.18

(Continued)

TABLE 2] *(Continued)*

Baseline Variable	No Response (n = 104)	Clinical Response (Including Patients With Clinical Remission) (n = 397)	*P* Value
Bronchiectasis	24 (24)	101 (26)	.68
Cardiovascular disease	30 (30)	112 (29)	.73
Chronic rhinosinusitis	54 (55)	240 (62)	.22
COPD	25 (25)	79 (20)	.33
Diabetes	8 (8)	33 (8)	.61
Dysfunctional breathing	8 (8)	32 (8)	.93
EGPA	2 (2)	12 (3)	.58
Eosinophilic pneumonia	8 (9)	10 (3)	.01
GERD	30 (31)	119 (31)	.95
Nasal polyposis	37 (39)	166 (42)	.61
Obesity (BMI ≥ 30 kg/m^2)	34 (33)	107 (28)	.25
OSA syndrome	15 (15)	42 (11)	.23
Psychiatric disease	17 (17)	49 (13)	.24
Vocal cord dysfunction	2 (2)	7 (2)	.90

Data are presented as mean ± SD, No. (%), or median (25th percentile-75th percentile). ABPA = allergic bronchopulmonary aspergillosis; ACQ-6 = six-question Asthma Control Questionnaire; EGPA = eosinophilic granulomatosis with polyangiitis; FENO = fractional exhaled nitric oxide; GERD = gastro-esophageal reflux disease; mOCS = maintenance oral corticosteroid.

anti-IgE was on the market. Importantly, the real-life nature of the current study precludes head-to-head comparisons of biologic drug classes, as patient population characteristics will vary due to differences in indication criteria and clinical predictors of effect.

Although evidence from clinical trials has shown the clinical effects of biologic treatment on exacerbations, with reductions of 38% to 53%,[20-27] less established is the real-life effectiveness of biologic therapy on these outcomes. We report the effectiveness of biologic therapy on exacerbations to be even greater than that observed in the clinical studies with a reduction of 81%. We also observed improvements on the ACQ-6 score by a full point and a small improvement in lung function, for which the evidence is less consistent from the clinical studies. This may be explained by the fact that in the clinical setting, as opposed to in clinical trials, trained respiratory physicians are better at identifying patients likely to respond to biologic therapy. A thorough systematic assessment for other causes of poor asthma control is required prior to commencing a biologic treatment. Hence, patients with comorbidities and treatment barriers are better managed prior to commencing their biologic therapy, and their remaining burden of symptoms therefore is more likely to reflect asthma pathology that will respond to biologic therapy. On the other hand, clinical trials have shown effects on mOCS with dose reductions of 45% to 75%.[28-30] DSAR patients did not follow a specific algorithm of mOCS down-titration as was done in the clinical trials, and our results are therefore not directly comparable, but we found 45% fewer individuals using mOCS following 12 months of follow-up compared with baseline. This somewhat lower clinical effect of biologic therapies on mOCS in the current study may reflect a higher severity of asthma in real life in some patients who require mOCS for an extended period, and these patients may be too sick to enter the clinical trials. It also highlights the difficulties in weaning off patients treated with long-term mOCS and suggests that timely intervention with biologic therapies prior to sustained periods with dependency on mOCS is therefore warranted. In line with this, we also identified that FEV_1 was the most difficult domain to improve, suggesting that biologic therapy should ideally be initiated before the lung function has decreased to a level that is difficult to normalize.

A major strength of the current study is that it used an unselected cohort of > 500 patients treated with biologic therapies from a nationwide complete register, which includes all patients with severe asthma in Denmark treated with a biologic drug. We used a pragmatic definition of remission that follows the definition of "clinical remission on treatment" proposed by Menzies-Gow et al,[8] which includes normalization of disease parameters, in contrast to the less stringent definition of super-response that previous real-life studies have used.

TABLE 3] Baseline Characteristics Comparing Clinical Responders vs Patients Achieving Remission Following 12 Months of Treatment

Baseline Variable	Clinical Response (Excluding Patients With Clinical Remission) (n = 300)	Clinical Remission (n = 97)	*P* Value
Demographic variables			
Age, y	56 ± 14	56 ± 13	.85
Female	162 (54)	37 (38)	.01
BMI, kg/m^2	28 ± 6	26 ± 4	.001
Duration of disease, y	23 ± 19	18 ± 17	.02
Duration of disease ≥ 10 y	158 (67)	41 (51)	.01
Age at asthma onset, y	33 ± 21	38 ± 21	.04
Onset during childhood (age ≤ 18 y)	78 (31)	22 (25)	.25
Late onset (age ≥ 40 y)	101 (42)	45 (54)	.18
Smoking status			.40
Never smoked	152 (51)	55 (57)	
Previously smoked	141 (48)	41 (43)	
Currently smokes	3 (1)	0 (0)	
Pack-y	15 (5-25)	15 (6-22)	.91
Medication use			
Budesonide equivalent dose, μg	1,600 (800-1,600)	1,600 (800-2,000)	.53
mOCS[a]	122 (41)	24 (25)	.01
mOCS, median dose	10.00 (5.00-15.00)	7.50 (5.00-10.00)	.08
Biologic class			.04
Anti-IgE	31 (10)	3 (3)	
Anti-IL-5/IL-5R	225 (75)	73 (75)	
Anti-IL-4Rα	44 (15)	21 (22)	
Symptom control			
ACQ-6 score	2.67 ± 1.17	2.01 ± 1.26	< .001
ACQ-6 score ≤ 1.5[a]	39 (17)	36 (48)	< .001
Exacerbations in the past 12 months[a]	4.11 ± 2.91	3.73 ± 2.51	.26
Exacerbations in the past 12 months[a]	3.00 (2.00-5.00)	3.00 (2.00-5.00)	.32
Lung function			
FEV_1, L	2.10 (0.81)	2.78 (0.85)	< .001
FEV_1, percent predicted[a]	66 ± 21	83 ± 19	< .001
FEV_1/FVC	0.65 ± 0.16	0.68 ± 0.12	.03
Inflammatory markers			
Blood eosinophils, cells × 10^9/L	0.32 (0.13-0.58)	0.50 (0.25-0.75)	.01
Blood eosinophils ≥ 0.3 10^9/L	154 (55)	68 (72)	.001
IgE, IU/mL	132 (47-350)	182 (92-406)	.12
IgE ≥ 150 IU/mL	100 (47%)	43 (57%)	.16
F_{ENO}, ppb	31 (15-60)	36 (21-75)	.08
F_{ENO} ≥ 25 ppb	150 (60)	62 (68)	.16
Comorbidities			
ABPA	11 (4)	1 (1)	.19
Allergic rhinitis	160 (54)	46 (48)	.31
Atopic dermatitis	58 (20)	11 (12)	.07
Aspirin sensitivity	21 (7)	10 (11)	.29

(Continued)

TABLE 3] *(Continued)*

Baseline Variable	Clinical Response (Excluding Patients With Clinical Remission) (n = 300)	Clinical Remission (n = 97)	*P* Value
Bronchiectasis	80 (27)	21 (22)	.32
Cardiovascular disease	92 (31)	20 (21)	.06
Chronic rhinosinusitis	176 (60)	64 (67)	.20
COPD	70 (24)	9 (9)	.003
Diabetes	27 (9)	6 (6)	.38
Dysfunctional breathing	30 (10)	2 (2)	.01
EGPA	12 (4)	0 (0)	.05
Eosinophilic pneumonia	6 (2)	4 (4)	.24
GERD	97 (33)	22 (23)	.06
Nasal polyposis	114 (38)	52 (54)	.01
Obesity (BMI ≥ 30 kg/m^2)	94 (32)	13 (13)	.001
OSA syndrome	36 (12)	6 (6)	.11
Psychiatric disease	42 (14)	7 (7)	.08
Vocal cord dysfunction	7 (2)	0 (0)	.13

Data are presented as mean ± SD, median (25th percentile-75th percentile), or n (%). ABPA = allergic bronchopulmonary aspergillosis; ACQ-6 = six-question Asthma Control Questionnaire; EGPA = eosinophilic granulomatosis with polyangiitis; FENO = fractional exhaled nitric oxide; GERD = gastro-esophageal reflux disease; mOCS = maintenance oral corticosteroid.
[a]Part of the definition for remission and therefore not considered a predictor of remission.

The major limitation of the current study concerns the lack of a control arm, restricting our ability to ascribe the observed treatment effects solely to the treatment. Other limitations of this study include missing data and the selection of patients with full information available to be included in the study population. There were 775 patients identified in DSAR that potentially could be included in the study, but only 501 (65%) were included due to missing baseline and/or follow-up data in the remaining patients. However, in those with baseline information available, the characteristics of excluded patients were very similar to patients who were included (data not shown).

In the current cohort, remission was achievable in approximately one in five patients. The chance of remission seemed to be better with earlier initiation of biologic therapy; that is, in patients with shorter disease duration and less severe disease with less airway remodeling and fixed airflow obstruction, and less use of mOCS. These findings suggest that earlier initiation of biologic therapies may translate into better short-term treatment outcomes. Naturally, the next step is to understand whether achieving remission also translates into better long-term outcomes, sustained asthma control and preserved lung function, and ultimately the ability to reduce or stop biologic therapy. Prospective severe asthma cohorts such as DSAR,[12] and

TABLE 4] Baseline Predictors of Clinical Remission After 12 Months of Biologic Therapy Analyzed in a Multivariate Logistic Regression Model With Remission as the Outcome

Predictors	OR (95% CI)	*P* Value
Sex		.13
Male	1.57 (0.88-2.83)	
Female	1.00 (Reference)	
BMI (kg/m^2) (1 unit increase)	0.92 (0.86-0.99)	.02
Duration of disease (1 y increase)	0.98 (0.97-0.99)	.047
Blood eosinophil count (doubling concentration)	1.18 (0.98-1.42)	.09
FENO (doubling concentration)	1.02 (0.81-1.27)	.88

FENO = fractional exhaled nitric oxide.

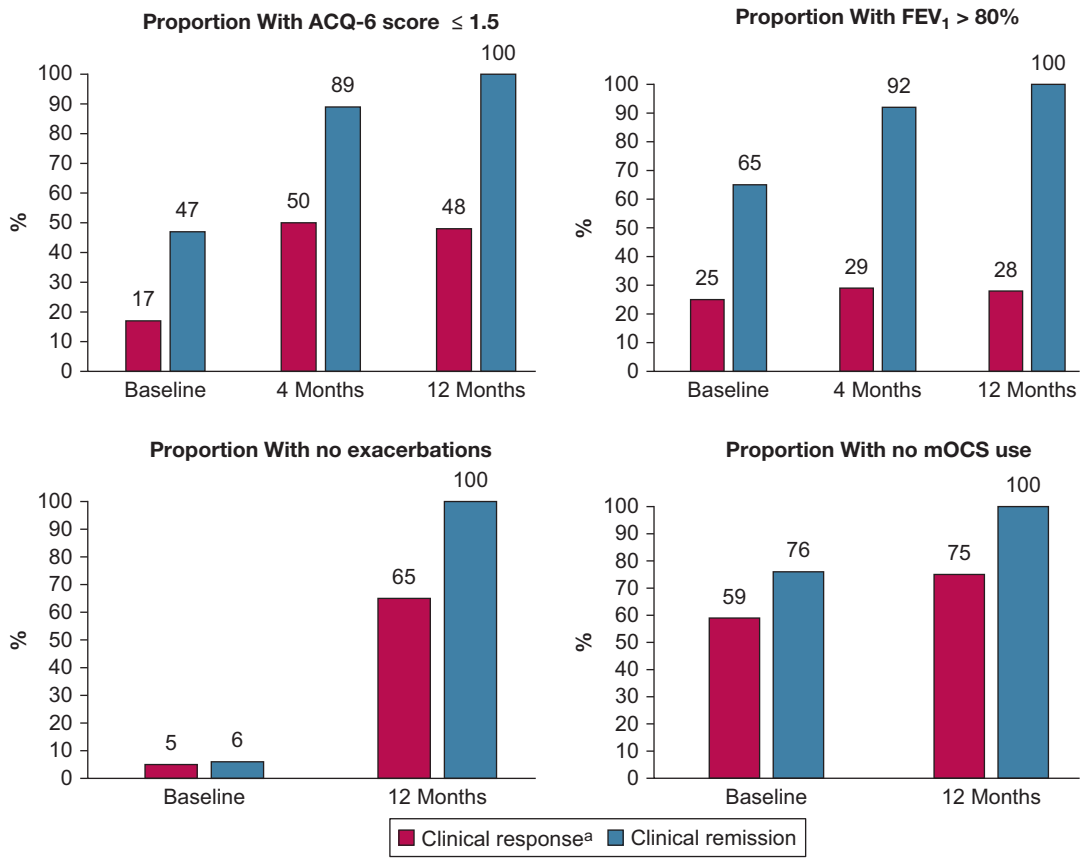


Figure 4 – *Temporal response in patients with clinical response and clinical remission: Proportion of patients with ACQ-6 score ≤ 1.5, FEV_1 ≥ 80%, no exacerbations, and no maintenance oral corticosteroid use at 4 and 12 months of follow-up. ACQ-6 = six-question Asthma Control Questionnaire; mOCS = maintenance oral corticosteroid.*

international collaboration such as Severe Heterogeneous Asthma Research Collaboration, Patient-Centered (SHARP)[31,32] and the International Severe Asthma Register (ISAR)[33,34] provide unique opportunities to study these questions. Furthermore, the importance of achieving an immunologic and pathophysiological remission is another key focus, currently studied by research initiatives such as the Taxonomy, Treatment, Targets and Remission (3TR) consortium,[35] in which real-life patients commenced on biologic therapy undergo thorough biologic sampling in addition to the prospective clinical assessments. Together, these concerted efforts will significantly strengthen our ability to further improve the outlook for patients with severe asthma in the coming years as we move into the era of disease modification in asthma through targeted immune-modifying treatments.

Interpretation

Using real-life data from 501 patients from the nationwide complete DSAR, we observed that most patients (79%) commencing biologic therapy obtained a favorable response in the outcome that set the indication for biologic therapy following 12 months of treatment. Furthermore, clinical remission on treatment was an achievable treatment goal, with 19% of patients going into remission following 12 months of treatment. Importantly, the chance of remission was better in patients with shorter disease duration and less severe disease, suggesting that early intervention is important for achieving optimal results. Next, the long-term clinical impact of achieving clinical remission on treatment needs to be explored.

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