

Original Article

Long-Term Therapy Response to Anti-IL-5 Biologics in Severe Asthma—A Real-Life Evaluation

Katrien Eger, MD^a, Johannes A. Kroes, MSc^b, Anneke ten Brinke, MD, PhD^c, and Elisabeth H. Bel, MD, PhD^a *Amsterdam and Leeuwarden, The Netherlands*

What is already known about this topic? Real-life data about long-term effects of anti-IL-5 treatment in patients with severe asthma are limited. Many questions about super responders and nonresponders, predictors of response, and residual disease manifestations are still unanswered.

What does this article add to our knowledge? In real-life, a small proportion of patients with specific characteristics show super response to long-term anti-IL-5 treatment. Most partial responders show impaired lung function or uncontrolled sinonasal disease, causing physicians to switch between biologics.

How does this study impact current management guidelines? Although anti-IL-5 biologics effectively reduce asthma exacerbations and oral glucocorticoid use in patients with eosinophilic asthma, in real-life many patients continue to suffer from bothersome disease manifestations despite anti-IL-5 treatment and these may require additional therapies.

BACKGROUND: Patients with severe eosinophilic asthma show different responses to various anti-IL-5 biologics, ranging from super response to nonresponse. Residual disease manifestations observed in partial responders may prompt physicians to switch between biologics. More data on response, switches, and residual disease manifestations are needed to improve personalized treatment.

OBJECTIVE: To assess (1) prevalences and predictors of super, partial, and nonresponders to long-term anti-IL-5 treatment, (2) frequency and reasons for switches between anti-IL-5 biologics, and (3) nature of residual disease manifestations. **METHODS:** In this 2-year follow-up study, patients with severe asthma were included who initiated an anti-IL-5 biologic (mepolizumab, reslizumab, benralizumab) ($n = 114$). Patient characteristics (clinical, functional, inflammatory) and comorbidities were collected at baseline and 2-year follow-up. “Super responders” showed no residual disease manifestations at 2-year follow-up, “partial responders” experienced residual disease manifestations, and “nonresponders” discontinued anti-IL-5 treatment after less than 2 years because of clinical worsening.

RESULTS: After 2-year anti-IL-5 treatment, 14% of patients were super responders, 69% partial responders, and 11% nonresponders. Super response was predicted by shorter asthma duration and higher FEV₁, and tended to be associated with adult-onset asthma, absence of nasal polyps, and lower body mass index. Switches between anti-IL-5 biologics occurred frequently (41%). After 2-year treatment, most common residual disease manifestations included impaired lung function (59%), uncontrolled sinonasal disease (58%), and uncontrolled asthma symptoms (48%).

CONCLUSIONS: After 2 years of anti-IL-5 treatment, a favorable response was found in 83% of patients with severe asthma, including a super response in 14%. Most partial responders show impaired lung function or uncontrolled sinonasal disease, causing physicians to switch between biologics. © 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Asthma; Benralizumab; Biologic therapy; Mepolizumab; Reslizumab

^aDepartment of Respiratory Medicine, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands

^bDepartment of Clinical Pharmacy and Pharmacology, Medical Center Leeuwarden, Leeuwarden, the Netherlands

^cDepartment of Respiratory Medicine, Medical Center Leeuwarden, Leeuwarden, the Netherlands

The Registry of Adult Patients with Severe asthma for Optimal Disease management (RAPSDI) is financially supported by an unrestricted grant from GlaxoSmithKline B.V., Netherlands; Novartis Pharma B.V., Netherlands; AstraZeneca, Netherlands; Sanofi/Genzyme Europe B.V., Netherlands; TEVA Nederland B.V., Netherlands. None of these sources had a role in this specific study.

Conflicts of interest: K. Eger has nothing to declare. J. A. Kroes reports a grant from AstraZeneca. A. ten Brinke reports institutional grants from GlaxoSmithKline (GSK), Teva, and Astra Zeneca outside the submitted work and participated in advisory boards for AstraZeneca, Teva, and Sanofi Regeneron. E. H. Bel reports

grants and personal fees from AstraZeneca, GSK, Novartis, Chiesi, Sanofi/Regeneron, Teva, and Serna outside the submitted work.

Received for publication July 23, 2020; revised September 22, 2020; accepted for publication October 2, 2020.

Available online ■■

Corresponding author: Katrien Eger, MD, Amsterdam UMC, University of Amsterdam, Department of Respiratory Medicine F5-260, Meibergdreef 9, 1105 AZ Amsterdam. E-mail: k.a.eger@amsterdamumc.nl.

2213-2198

© 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.jaip.2020.10.010>

Abbreviations used

FENO- Fractional exhaled nitric oxide

NP- Nasal polyp

OCS- Oral corticosteroid

INTRODUCTION

Severe asthma is a debilitating disease associated with persistent symptoms, poor quality of life, and frequent use of oral corticosteroids (OCSs), which are known to increase the risk of comorbidities.^{1,2} Fortunately, the new steroid-sparing biologics for severe asthma targeting IL-5 (mepolizumab and reslizumab) or IL-5 receptor (benralizumab) have a large positive impact on the lives of many patients.³⁻⁵

However, the response to these anti-IL-5 biologics does not seem to be equal in every patient. Some patients reach complete asthma control ("super responders"), whereas others experience residual disease manifestations ("partial responders") or show no improvement or even clinical worsening ("nonresponders").⁶⁻⁸ The underlying mechanisms of these different responses are not yet known. Moreover, responses may vary between the different anti-IL-5 biologics, which may be due to differences in target, mode of administration, or dosing (interval). Perhaps that is why clinicians in real-life may decide to switch between treatments in those patients who have an incomplete response to achieve optimal disease control.⁹

At present, there is limited data about long-term effects of anti-IL-5 treatment in patients with severe asthma in real life.^{6,7,10,11} Many questions about responders and nonresponders, predictors of response, and residual disease after blocking the IL-5 pathway are still unanswered. Answers to these questions could help to better understand the pathophysiology of severe asthma, and thus further improve personalized treatment.

The aims of the present study were first, to assess the prevalence of "super responders," "partial responders," and "nonresponders" to long-term (2 years) anti-IL-5 treatment; second, to assess predictors of nonresponse and super response; third, to evaluate the proportion of patients who had switched between anti-IL-5 biologics and why; and fourth, to characterize residual disease manifestations in partial responders. We used prospective real-life data from a multicenter cohort of 114 patients with severe eosinophilic asthma treated with different anti-IL-5 biologics (mepolizumab, reslizumab, benralizumab) for more than 2 years.

METHODS**Design and patient selection**

Patients with severe asthma visiting the pulmonary outpatient clinics from 2 Dutch asthma expertise centers (Amsterdam University Medical Center and Medical Center Leeuwarden) were asked to participate in this study. Patients were diagnosed with severe asthma according to European Respiratory Society/American Thoracic Society guideline criteria¹² and were included in the Registry of Adult Patients with Severe asthma for Optimal Disease management (RAPSODI) or a similar registry running in Medical Center Leeuwarden, after having provided informed consent. For inclusion in the present study, patients had to be treated with 1 or more biologic against IL-5 (mepolizumab and/or reslizumab and/or benralizumab) and had to have started anti-IL-5 treatment in the period April 2016 to December 2017. Patients were excluded if they

were lost to follow-up, if they had interrupted anti-IL-5 treatment for more than 3 months during the follow-up period, or if they had previously received anti-IL-5 treatment in a trial. At baseline and at 2-year follow-up, clinical, functional, inflammatory, and comorbidity data were derived from the registries and supplemented with data from electronic patient files.

Measurements

Clinical characteristics: Demographic characteristics, asthma duration, 6-item Asthma Control Questionnaire score.¹³

Surrogate inflammatory markers/anti-inflammatory treatments: Peripheral blood eosinophils, fractional exhaled nitric oxide (FENO, NIOX System, Aerocrine, Sweden),¹⁴ maintenance dose of OCS, OCS bursts or episodes of doubling the OCS maintenance dose for 3 days or more in the last 3 months, IgE.

Lung function: FEV₁ measured according to standardized methods.¹⁵

Comorbidities: Chronic rhinosinusitis and presence of nasal polyps (NPs) or chronic otitis were diagnosed by an ear-nose-throat specialist; allergic rhinoconjunctivitis was diagnosed by elevated specific IgE testing combined with a history of allergic symptoms; and atopic dermatitis was diagnosed on the basis of patient's history and physical examination. Adrenal insufficiency was confirmed by low morning cortisol levels (<150 nmol/L) or inability to lower OCS dose because of severe adrenal insufficiency symptoms such as severe fatigue and nausea.

Changes in anti-IL-5 treatments: Frequency of switches between anti-IL-5 treatments, reasons for switches (eg, persistent asthma or sinonasal symptoms including exacerbations, persistent airflow limitation, inability to taper or stop OCS, adverse effects), or discontinuation of anti-IL-5 treatments.

Definitions of responders

Super responders were defined as patients with complete control of asthma after 2 years of anti-IL-5 treatment, as shown by no chronic OCS use, no OCS bursts in the past 3 months, ACQ score less than 1.5, FEV₁ greater than or equal to 80% predicted, FENO less than 50 ppb, and complete control of comorbidities (chronic rhinosinusitis, NP, chronic otitis, allergic rhinoconjunctivitis, and atopic dermatitis).

Nonresponders were defined as patients who discontinued anti-IL-5 treatment after less than 2 years because of clinical worsening with either increased symptoms, decreased FEV₁, or increased OCS use.

Partial responders were defined as patients who did not fulfill the criteria of nonresponders or superresponders after 2 years of anti-IL-5 treatment.

Analyses

First, the prevalences of super responders, partial responders, and nonresponders were calculated. Patient characteristics of the 3 responder groups at baseline were evaluated using descriptive statistics. Blood eosinophil levels (expressed as cells $\times 10^9/L$) in patients on chronic OCS therapy were corrected for the daily maintenance OCS dose (mg/d) with the following calculation: (eosinophils) $\times (1.07)^{(\text{OCS dose})}$.¹⁶ Differences between nonresponders or super responders versus the other patients were analyzed by using Mann-Whitney *U*, χ^2 , or Fisher exact test when applicable. Differences in patient characteristics with a *P* value less

TABLE I. Patient characteristics at baseline and 2-y follow-up

Characteristic	All patients (n = 114)	Nonresponders (n = 12)	Partial responders (n = 79)		Super responders (n = 16)	
	Baseline	Baseline	Baseline	2-y follow-up	Baseline	2-y follow-up
Clinical characteristic						
Age* (y)	55 (46-64)	53 (46-70)	56 (45-63)	—	53 (49-62)	—
Sex: male, %	54	50	51	—	67	—
Body mass index* (kg/m ²)	27 (25-31)	27 (25-30)	28 (25-32)	—	25 (23-29) [†]	—
Former smoker, %	43	42	43	—	53	—
Duration of asthma* (y)	15 (5-30)	21 (8-38)	16 (6-34)	—	6 (4-12) [†]	—
Asthma onset ≥18 y, %	70	50 [†]	71	—	93 [†]	—
ACQ-6 score* (n = 75)	2.50 (1.50-3.17)	2.67 (2.10-3.50)	2.50 (1.50-3.33)	1.33 (0.67-2.17)	2.33 (1.17-2.33)	0.17 (0.00-0.83)
ACQ-6 score ≥1.5, %	77	89	78	48	71	0
Surrogate inflammatory markers						
OCS maintenance therapy, %	68	75	70	32	63	0
OCS dose*, [‡] (mg/d)	10 (7.5-15)	7.5 (6.25-12.5)	10 (7.5-15)	10 (5-13.75)	10 (5-15)	NA
≥1 OCS burst last 3 mo, %	56	56	55	24	63	0
Eosinophils* (10 ⁹ /L)	0.51 (0.27-0.96) [§]	0.36 (0.19-0.69) [§]	0.57 (0.28-1.04) [§]	0.07 (0.02-0.10)	0.46 (0.25-0.53) [§]	0.07 (0.02-0.12)
FENO* (ppb)	34 (24-52)	36 (19-65)	34 (25-56)	35 (23-54)	32 (22-40)	24 (11-35)
FENO >50 ppb, %	26	33	27	26	19	0
Total IgE* (IU/mL) (n = 96)	114 (35-299)	95 (29-131)	116 (40-319)	NA	147 (38-260)	NA
Lung function						
FEV ₁ *, % predicted	76 (61-93)	76 (63-101)	74 (61-90)	73 (61-94)	94 (68-106) [†]	98 (90-113)
FEV ₁ <80%, %	56	58	61	59	31 [†]	0
Uncontrolled comorbidities, %						
CRS	69	67	72	57	56	0
NPs	23	25	26	19	6 [†]	0
Chronic otitis	12	8	14	12	6	0
Atopic dermatitis	6	0	9	7	0	0
Allergic rhinoconjunctivitis	26	33	26	23	19	0
Adrenal insufficiency	NA	NA	NA	10	NA	0

ACQ-6, 6-Item Asthma Control Questionnaire; CRS, chronic rhinosinusitis; FENO, fractional exhaled nitric oxide; IQR, interquartile range; NA, not applicable or not available. *Median (IQR).

[†] $P < .15$ (super responders or nonresponders vs other patients).

[‡]OCS dose is provided as prednisone-equivalent for patients on chronic OCS therapy.

[§]Eosinophil levels in patients on chronic OCS therapy are corrected for OCS dose.¹⁶

than .15 from this analysis were tested in a binary logistic regression analysis to assess whether these variables were predictors of nonresponse or super response adjusted for age and sex.

Second, the prevalence of patients who switched between anti-IL-5 biologics was assessed, both for the entire cohort and for the various responder groups separately. Next, the proportions of the different categories of reasons for these switches were evaluated. Descriptive statistics at 2-year follow-up were used to evaluate residual disease manifestations in partial responders.

Differences were considered significant if P values were less than .05. SPSS software (SPSS Statistics, version 26; IBM Corporation, Armonk, NY) was used to perform the statistical analyses.

RESULTS

Patient selection

Of 141 patients with severe asthma in the registries who had initiated anti-IL-5 treatments (mepolizumab, reslizumab, benralizumab) in the period April 2016 to December 2017, 2 patients were lost to follow-up, 19 patients were participants of previous anti-IL-5 trials, and 6 patients had interruptions in anti-IL-5 treatment for more than 3 months during the 2-year period. The 114 patients included in the analyses were mostly

middle-aged, had an adult-onset asthma, a high prevalence of sinonasal disease, a high ACQ score, and two-third of patients used OCS maintenance therapy at baseline (Table I, left panel).

Prevalence of super responders, partial responders, and nonresponders

After 2 years of anti-IL-5 treatment, 95 of 114 patients (83%) still used anti-IL-5 biologics and 19 patients (17%) had discontinued this treatment. Sixteen patients (14%) met the definition of super responder, 79 (69%) were partial responders, and 12 (11%) were nonresponders (Figure 1). Nonresponders had received a median of 8 administrations of an anti-IL-5 biologic (interquartile range, 4-15). Anti-IL-5 treatment was discontinued for other reasons in 7 patients (6%), 3 of which discontinued because of adverse effects.

Predictors of response to long-term anti-IL-5 therapy

Baseline characteristics of super responders, partial responders, and nonresponders to 2-year anti-IL-5 treatment are presented in Table I. Nonresponders could not be distinguished from the other groups by any of the baseline characteristics, although there was a trend toward lower blood eosinophils (P value = .183) and

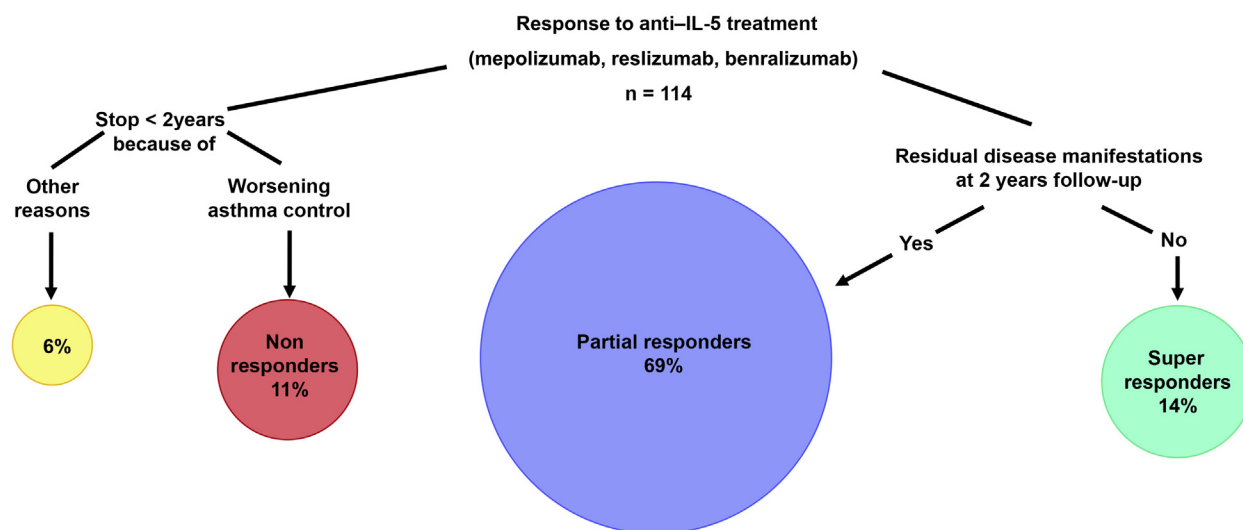


FIGURE 1. Prevalence of super responders, partial responders, and nonresponders after 2 years of treatment with anti-IL-5 biologics for severe eosinophilic asthma. In this observational cohort study, 11% of patients could be labeled as nonresponders, 69% as partial responders, and 14% as super responder after 2 years of anti-IL-5 treatment for severe eosinophilic asthma. Six percent of patients discontinued anti-IL-5 treatment after less than 2 years for other reasons.

TABLE II. Predictors of super response to long-term anti-IL-5 biologics

Predictor	Adjusted OR*	95% CI	P value
Asthma onset ≥ 18 y	5.961	0.706-50.311	.101
Absence of NPs	5.950	0.721-49.082	.098
FEV ₁ $\geq 80\%$ predicted	3.708	1.120-12.284	.032
Asthma duration < 10 y	3.572	1.093-11.673	.035
BMI < 25	2.675	0.820-8.719	.103

BMI, Body mass index; OR, odds ratio.

*OR adjusted for age and sex.

more frequent asthma that started before age 18 years (P value = .135). In a regression analysis, no significant predictors of nonresponse could be identified. Super responders however showed a significantly shorter duration of asthma (P value = .009) and a higher FEV₁ % predicted (P value = .024) as compared with the other patients, and tended to have a lower body mass index (P value = .091), more frequently asthma that had started in adulthood (P value = .104), and less often NPs (P value = .112). After adjustment for age and sex, FEV₁ % predicted and asthma duration were predictors of super response, with an odds ratio of 3.7 and 3.5, respectively (Table II). Further adjustment for potential confounders was not possible due to the small number of super responders.

Switches between anti-IL-5 biologics

Of the 114 included patients, 67 (59%) did not switch between anti-IL-5 biologics during the study period, 39 (34%) switched to another anti-IL-5, and 8 (7%) made 2 switches. The frequency of switches was not significantly different between super responders, partial responders, or nonresponders (P value = .670; Figure 2). Persistent asthma or sinonasal symptoms, including exacerbations, were the most frequently

reported reasons for switching between anti-IL-5 biologics (53%), followed by inability to taper or stop OCS (28%), or persistent airflow limitation (17%). Only a small percentage of patient switched because of adverse effects (5%).

Residual disease manifestations in partial responders after 2-year anti-IL-5 treatment

The residual disease manifestations in partial responders are summarized in Figure 3. The most prevalent residual conditions were persistent airflow obstruction (59%), symptoms of ear-nose-throat pathology including chronic rhinosinusitis, NPs, or chronic otitis (58%), and uncontrolled asthma symptoms (48%). After 2 years of treatment, 32% of patients still used maintenance OCS, of which about one-third were diagnosed with adrenal insufficiency by their treating physician. More detailed information on outcomes in both partial responders and super responders, including 6-item Asthma Control Questionnaire scores, FENO levels, and FEV₁ % predicted values, can be found in Table I.

DISCUSSION

In this real-life study, 83% of patients with severe eosinophilic asthma had a favorable response to long-term (2-year) anti-IL-5 treatment, although frequent switches between biologics occurred. Super response was observed in 14% of patients and was predicted by shorter asthma duration and higher FEV₁, and tended to be associated with adult-onset asthma, absence of NPs, and lower body mass index. Partial responders (69%) experienced residual disease manifestations even after 2 years of treatment, including inadequately controlled symptoms of asthma or rhinosinusitis, persistent airflow limitation, or OCS dependency. Only 11% of patients qualified as nonresponders.

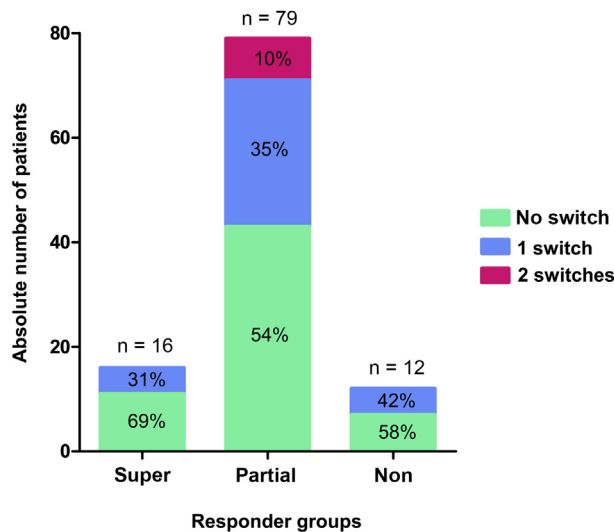


FIGURE 2. Frequency of switches between anti-IL-5 treatments in the different response groups. Figure 2 shows the number of switches between anti-IL-5 treatments in super responders, partial responders, and nonresponders. There was no significant difference in the number of switches between the different responder groups ($P = .670$).

After 2 years of anti-IL-5 treatment 14% of patients were completely free of any disease manifestation, which we labeled “super responders.” Other studies focusing on super responders found higher rates (20%-28%), but this can be explained by the less stringent criteria of super response in these studies.^{6,7} For example, we found that many patients with a favorable response regarding OCS use or asthma exacerbations still suffered from (severely) impaired lung function or uncontrolled sinus disease, even after 2 years of treatment.

Several studies have looked at predictors of (super-)response to anti-IL-5 treatment, but here again response was mostly defined in terms of reduction of exacerbations or OCS use.^{17,18} For these outcome parameters, higher eosinophil counts or higher exacerbation rates seem to be the best predictors. However, despite the small numbers in our study, we may carefully suggest that the profile of a true super responder to long-term anti-IL-5 biologics is an adult with a relatively short duration of eosinophilic asthma, without NPs, chronic airflow limitation, or overweight. Further research in larger cohorts is needed to confirm these findings.

The observed heterogeneity of response to anti-IL-5 treatments can have several causes. First, it may be related to the medication itself. Individual differences in pharmacokinetics and resulting plasma drug levels are currently not taken into account, while therapeutic drug monitoring is common practice in other chronic conditions treated with mAbs.¹⁹ In addition, mAbs in general can induce immunogenicity with subsequent formation of antidrug antibodies, which in theory could lead to secondary loss of response.^{20,21} Moreover, dosing of medication is not tailored to the degree of inflammation in the airways, which may lead to underdosing in patients with the most severe inflammation.^{9,22} Second, incomplete responses to anti-IL-5

treatment could be due to irreversible remodeling of upper and lower airways or irreversible adrenal insufficiency after long-term OCS use.^{23,24} Third, residual asthma symptoms without evidence of eosinophilic inflammation may be caused by comorbidities such as dysfunctional breathing, obesity, deconditioning, bronchiectasis, or cardiovascular disease. Lastly, the observed residual disease manifestations may result from ongoing activation of non-IL-5-driven inflammatory pathways, such as the IL-4/IL-13 pathway.²⁵⁻²⁸ It is even conceivable that blocking one inflammatory pathway activates another.²⁹

This study has strengths and limitations. Strengths include first, that it is a non-pharma-sponsored real-life study of a relatively large group of patients on long-term treatment with various anti-IL-5 biologics. Second, it is the only study with documentation of switches between treatments and reasons for switches. Third, we used a composite treatment response definition, covering all relevant asthma-related parameters.

The limitations of this study are those that generally apply to real-world studies; for example, no standardized way of recording, possibility of incompleteness of data, and so forth. However, we believe that these limitations were relatively insignificant because patients were recruited in 2 centers that have extensive experience in performing drug trials in patients with severe asthma. Another limitation was that in this real-life study it was not possible to determine which anti-IL-5 biologic performed best, because the order of introduction of the various anti-IL-5 biologics in the Netherlands was an important bias factor. Indeed, previous treatment with one biologic may have affected the response to the next biologic. A randomized head-to-head comparison would be more appropriate for this purpose.

An important clinical implication of our study is that although the anti-IL-5 biologics lead to an impressive clinical response in most patients, physicians should realize that many are still left with unresolved disease manifestations such as impaired lung function, nasal polyposis, or persistent OCS dependency, likely indicating active airway inflammation that may require additional local or systemic treatment.³⁰ It seems therefore advisable to evaluate the therapeutic response in a systematic way taking into account therapy adherence as well as all domains of disease including comorbidities and inflammatory biomarkers such as FENO.^{31,32}

CONCLUSIONS

This study shows that the vast majority of patients with severe asthma respond favorably to anti-IL-5 biologics after 2 years of treatment, with 14% super responders and only a small proportion of nonresponders. However, residual disease manifestations are common and vary from asthma exacerbations, OCS dependency, and persistent airflow limitation, to uncontrolled asthma-related comorbidities. This incomplete response often causes physicians to switch between anti-IL-5 biologics in their patients, or switch to biologics targeting other pathways such as the IL-4/IL-13 pathway. Presumably, new future asthma biologics that simultaneously block multiple inflammatory pathways will eventually provide a more complete resolution of severe asthma symptoms and comorbidities.

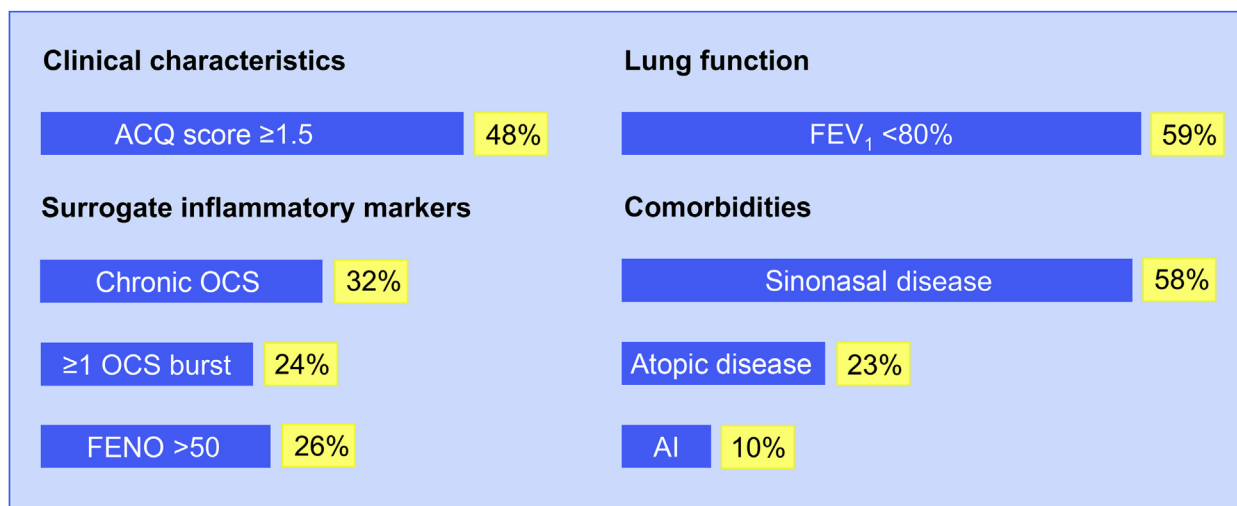


FIGURE 3. Residual disease manifestations in partial responders after 2 years of anti-IL-5 treatment. OCS bursts were recorded less than 3 months before 2-year follow-up. Sinonasal disease is uncontrolled chronic rhinosinusitis, or presence of NPs or chronic otitis. Atopic disease is uncontrolled allergic rhinoconjunctivitis or atopic dermatitis. ACQ-6, 6-Item Asthma Control Questionnaire; AI, adrenal insufficiency.

REFERENCES

- Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med* 2017;377:965-76.
- Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. *Eur Respir J* 2018;52:1800703.
- Ortega HG, Liu MC, Pavord ID, Brusselle GG, Fitzgerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-207.
- Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355-66.
- Nair P, Bardin P, Humbert M, Murphy KR, Hickey L, Garin M, et al. Efficacy of intravenous reslizumab in oral corticosteroid-dependent asthma. *J Allergy Clin Immunol Pract* 2020;8:555-64.
- Harvey ES, Langton D, Katelaris C, Stevens S, Farah CS, Gillman A, et al. Mepolizumab effectiveness and identification of super-responders in severe asthma. *Eur Respir J* 2020;55:1902420.
- Kavanagh JE, d'Ancona G, Elstad M, Green L, Fernandes M, Roxas C, et al. Real-world effectiveness and the characteristics of a 'super-responder' to mepolizumab in severe eosinophilic asthma. *Chest* 2020;158:491-500.
- Mukherjee M, Forero DF, Tran S, Boulay ME, Bertrand M, Bhalla A, et al. Sub-optimal treatment response to anti-IL-5 monoclonal antibodies in severe eosinophilic asthmatics with airway autoimmune phenomena. *Eur Respir J* 2020;56:2000117.
- Mukherjee M, Paramo FA, Kjarsgaard M, Salter B, Nair G, LaVigne N, et al. Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. *Am J Respir Crit Care Med* 2018;197:38-46.
- Schleich F, Graff S, Nekoe H, Moermans C, Henket M, Sanchez C, et al. Real-world experience with mepolizumab: does it deliver what it has promised? *Clin Exp Allergy* 2020;50:687-95.
- Taillé C, Chanez P, Devouassoux G, Didier A, Pison C, Garcia G, et al. Mepolizumab in a population with severe eosinophilic asthma and corticosteroid dependence: results from a French early access programme. *Eur Respir J* 2020;55:1902345.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk P, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-73.
- Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553-8.
- Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al, on behalf of the American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications. An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FE NO) for Clinical Applications. *Am J Respir Crit Care Med* 2011;184:602-15.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- Prazma CM, Bel EH, Price RG, Bradford ES, Albers FC, Yancey SW. Oral corticosteroid dose changes and impact on peripheral blood eosinophil counts in patients with severe eosinophilic asthma: a post hoc analysis. *Respir Res* 2019;20:1-4.
- FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med* 2018;6:51-64.
- Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016;4:549-56.
- Kroes JA, Zielhuis SW, Van Roon EN, Brinke A. Prediction of response to biological treatment with monoclonal antibodies in severe asthma. *Biochem Pharmacol* 2020;179:113978.
- Chaigne B, Watier H. Monoclonal antibodies in excess: a simple way to avoid immunogenicity in patients? *J Allergy Clin Immunol* 2015;136:814-6.
- Cormier M, Chabouille S, Lemiere C. Secondary loss of response to mepolizumab in severe eosinophilic asthma. *J Allergy Clin Immunol Pract* 2020;8:736-8.
- Peters MC, Kerr S, Dunican EM, Woodruff P, Fajt M, Levy B, et al. Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 2019;143:104-113.e14.
- Nanzer A, Chowdhury A, Raheem A, Roxas C, Fernandes M, Thomson L, et al. Prevalence and recovery of adrenal insufficiency in steroid-dependent asthma patients receiving biologic therapy. *Eur Respir J* 2020;56:1902273.
- Rowan NR, Naclerio RM. Persistence of sinonasal disease despite mepolizumab. *J Allergy Clin Immunol Pract* 2020;8:1550-5.
- Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol* 2019;144:1-12.
- Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol* 2015;15:57-65.
- Bachert C, Gevaert P, Hellings P. Biotherapeutics in chronic rhinosinusitis with and without nasal polyps. *J Allergy Clin Immunol Pract* 2017;5:1512-6.

28. Shrimanker R, Pavord ID, Yancey S, Heaney LG, Green RH, Bradding P, et al. Exacerbations of severe asthma in patients treated with mepolizumab. *Eur Respir J* 2018;52:1801127.
29. Choy DF, Hart KM, Borthwick LA, Shikotra A, Nagarkar D, Siddiqui S, et al. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma. *Sci Transl Med* 2015;7:301ra129.
30. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016;47:410-9.
31. Global Initiative for Asthma. Difficult-to-treat & severe asthma in adolescent and adult patients. A GINA pocket guide for health professionals. V2.0, April 2019. Available at: <https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf>. Accessed April 14, 2020.
32. d'Ancona G, Kavanagh J, Roxas C, Green L, Fernandes M, Thomson L, et al. Adherence to corticosteroids and clinical outcomes in mepolizumab therapy for severe asthma. *Eur Respir J* 2020;55:1902259.