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Original Article

Real-World Effectiveness of IL-5/5Ra Targeted Biologics in Severe Eosinophilic Asthma With Comorbid Bronchiectasis

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What is already known about this topic? Anti-IL-5/5Ra biologics have been shown to reduce the exacerbation rate and oral corticosteroid (OCS) use in severe eosinophilic asthma. How coexisting bronchiectasis, a common comorbidity in severe asthma, affects the response to these biologics is unknown.

What does this article add to our knowledge? This real-world study shows that anti-IL-5/5Ra biologics effectively reduce the exacerbation frequency and daily maintenance and cumulative OCS dose in patients with severe eosinophilic asthma and comorbid bronchiectasis.

How does this study impact current management guidelines? The findings suggest that anti-IL-5/5Ra biologics should be considered as add-on therapy for patients with severe eosinophilic asthma regardless of comorbid bronchiectasis. This therapy may help reduce OCS exposure, which is particularly relevant in this patient group.

BACKGROUND: Bronchiectasis is a common comorbidity in patients with asthma and is associated with increased disease severity. In patients with severe eosinophilic asthma, biologics targeting IL-5/5Ra have beneficial effects on oral corticosteroid (OCS) use and exacerbation frequency. However, how coexisting bronchiectasis affects the response to such treatments is unknown.

OBJECTIVE: To evaluate the real-world effectiveness of anti-IL-5/5Ra therapy in patients with severe eosinophilic asthma and comorbid bronchiectasis on exacerbation frequency and daily maintenance and cumulative OCS dose.

METHODS: This real-world study evaluated data from 97 adults with severe eosinophilic asthma and computed tomography–confirmed bronchiectasis from the Dutch Severe

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Abbreviations used
ABPA- Allergic bronchopulmonary aspergillosis
ACQ-6- Six-item Asthma Control Questionnaire
CT- Computed tomography
OCS- Oral corticosteroid
RAPSODI- Dutch Registry of Adult Patients With Severe Asthma for Optimal Disease Management
RCT- Randomized controlled trial

Asthma Registry, who initiated anti-IL5/5Ra biologics (mepolizumab, reslizumab, and benralizumab) and had follow-up data for 12 months or greater. The analysis was performed for the total population and subgroups with or without maintenance OCS use.
RESULTS: Anti-IL-5/5Ra therapy significantly reduced exacerbation frequency in patients with maintenance OCS use as well as in those without it. In the year before biologic initiation, 74.5% of all patients had two or more exacerbations, which decreased to 22.1% in the follow-up year ($P < .001$). The proportion of patients on maintenance OCS decreased from 47% to 30% ($P < .001$), and in the OCS-dependent patients (n = 45) maintenance OCS dose decreased from median (interquartile range) of 10.0 mg/d (5-15 mg/d) to 2.5 mg/d (0-5 mg/d) after 1 year ($P < .001$).
CONCLUSIONS: This real-world study shows that anti-IL-5/5Ra therapy reduces exacerbation frequency and daily maintenance as well as the cumulative OCS dose in patients with severe eosinophilic asthma and comorbid bronchiectasis. Although it is an exclusion criterion in phase 3 trials, comorbid bronchiectasis should not preclude anti-IL-5/5Ra therapy in patients with severe eosinophilic asthma. © 2023 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2023;11:2724-31)

Key words: *Severe asthma; Bronchiectasis; Biologic therapy; Oral corticosteroids*

INTRODUCTION

Bronchiectasis is a common comorbidity in asthma. Actual numbers on the prevalence of bronchiectasis in asthma vary among studies at 5% to 40%, with a significantly higher prevalence in severe asthma compared with mild asthma.[1-3] In patients with severe asthma, concomitant bronchiectasis increases the risk for exacerbations and hospitalizations, decreases quality of life, and may worsen the prognosis.[4-6] In clinical practice, the severe asthma with bronchiectasis phenotype is often considered difficult to treat because it is more refractory to regular asthma treatment.[7] This poses a challenge to health care providers and is especially burdensome to affected patients.

Asthma and bronchiectasis are heterogeneous diseases in which separate phenotypes have been recognized[8,9] with different underlying inflammatory patterns, risk factors, and clinical outcomes. In severe asthma, most patients have a type 2-high subtype characterized by extensive eosinophilic airway inflammation, mediated by cytokines such as IL-4, IL-13, and especially IL-5. Although bronchiectasis has traditionally been associated with neutrophilic inflammation, recent studies show that inflammation in bronchiectasis is heterogeneous, in which a subset of patients exhibit eosinophilic inflammation, indicating a type 2 inflammatory process.[10-12]

Until recently, many patients with severe eosinophilic asthma depended on repeated or daily use of oral corticosteroids (OCS) to control the disease,[13-15] which put them at high risk for serious long-term side effects. Studies showed that OCS-related side effects are dose-dependent and associated with cumulative OCS exposure rather than mean daily OCS dose.[16,17] In patients with severe eosinophilic asthma and comorbid bronchiectasis, the use of OCS may be even more detrimental because it may contribute to the suppression of host immunity and increase the risk for bacterial or fungal infections or colonization.[18,19] Thus, there is a great need for OCS-sparing treatment for these patients, possibly through biologics, particularly those targeting IL-5, the major cytokine responsible for the recruitment and activation of eosinophils.

For patients with severe eosinophilic asthma without bronchiectasis, the efficacy of biologics targeting IL-5 (mepolizumab and reslizumab) or IL-5Ra (benralizumab) has been demonstrated in multiple phase 3 randomized controlled trials (RCTs)[20-22] and real-world studies.[23-25] These studies show that IL-5/5Ra-targeted therapy reduces the exacerbation rate and OCS use and improves asthma control and quality of life in many patients with severe eosinophilic asthma.[20-22,26] However, data on the effectiveness of IL-5/5Ra-targeted biologics in pa-

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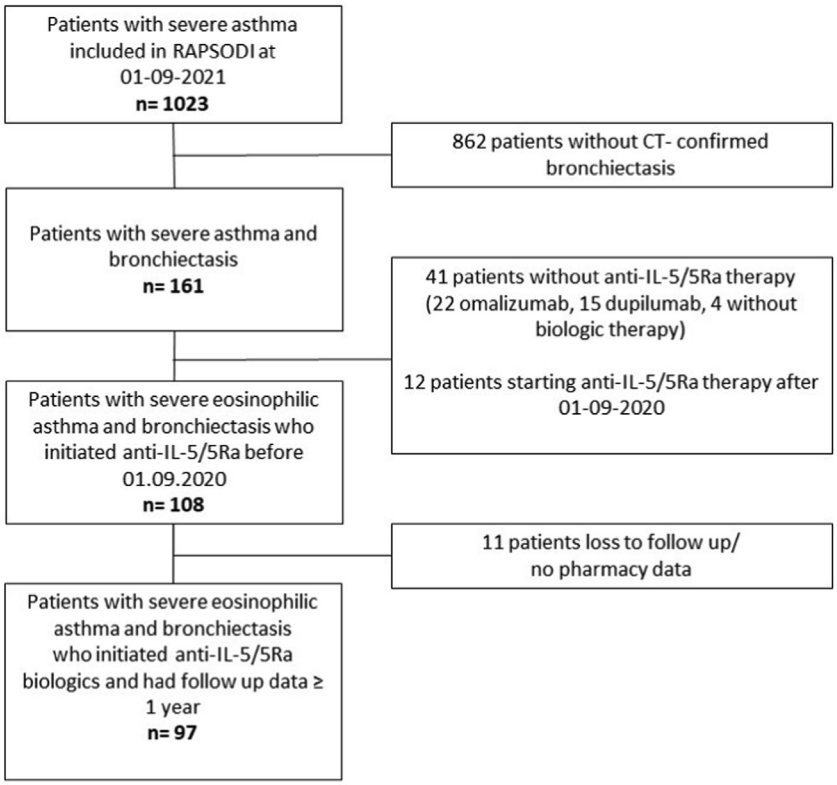

FIGURE 1. Patient selection. *CT*, computed tomography; *RAPSODI*, Dutch Registry of Adult Patients With Severe Asthma for Optimal Disease Management.

tients with severe asthma with comorbid bronchiectasis are scarce and limited to pilot studies with a limited sample size,[27] case series,[28-30] or studies of patients with concomitant allergic bronchopulmonary aspergillosis (ABPA).[31-35]

Therefore, in the current nationwide study, we evaluated the real-world effectiveness of IL-5/5Ra—targeted biologic therapy in patients with severe eosinophilic asthma and comorbid bronchiectasis on the asthma exacerbation frequency, daily and cumulative OCS dose, asthma control, and lung function. For analyses, we used real-world longitudinal patient data from the Dutch Registry of Adult Patients With Severe Asthma for Optimal Disease Management (RAPSODI).

METHODS

Study design and patient population

This was a real-world, nationwide, retrospective, observational, registry-based study. The study population consisted of all adult patients (aged 18 years and older) with severe asthma included in RAPSODI. Patients included in this registry have the diagnosis of severe asthma according to European Respiratory Society/American Thoracic Society criteria.[36] All are treated with high-dose inhaled corticosteroids combined with additional controller medication.

For the current study, we selected all patients with bronchiectasis registered as a comorbidity by the attending specialist and confirmed by computed tomography (CT). We included patients who initiated anti-IL-5/5Ra therapy (mepolizumab, reslizumab, and benralizumab) between December 1, 2015 and September 1, 2020 with available follow-up data at 12 months after initiation (Figure 1). For the outcome measurements of exacerbation frequency and OCS use, patients needed data for over 1 year before beginning anti-IL-5/5Ra treatment.

According to the Dutch Severe Asthma Guidelines, the inhaled medication dose, inhalation technique, and adherence should be optimized, patients should be monitored for at least 6 months by an asthma specialist before initiating biologic treatment, and anti-IL-5/5Ra eligibility should be based on blood eosinophils of 0.3×10^9 cells/L or greater, or 0.15×10^9 cells/L or greater for patients using OCS maintenance treatment.

Because it was likely that OCS use and the exacerbation rate mutually influence each other, we distinguished two groups of patients in the analysis: patients who did and those who did not receive maintenance OCS at anti-IL-5/5Ra treatment initiation. Patients were excluded if they were lost to follow-up or no pharmacy data were available.

This study used a pre-post approach. We compared characteristics and outcomes at 12 months after anti-IL-5/5Ra treatment initiation with those for the same asthma patients at the time of anti-IL-5/5Ra treatment initiation. Informed consent for this study was collected at registry enrollment. The Medical Ethics Review Committee of Leiden, Den Haag, Delft, waived a formal approval from a medical ethics committee according to Dutch legislation (Reference No. G21.158).

Data source

We retrieved data on patients with severe asthma from 19 Dutch hospitals from the RAPSODI registry, which is based on two sources: annual electronic case report forms (135 CASTOR EDC

platform, Amsterdam, the Netherlands), and 3-monthly electronic patient questionnaires (PatientCoach; Leids Universitait Medisch Centrum, Leiden).[23] In addition, to assess cumulative OCS exposure, we requested the systemic corticosteroid dispensing data (ATC-code H02AB) for 12 months before and 12 months after anti-IL-5/5Ra initiation from each patient's pharmacy. We verified that the patient consented to the Dutch National Exchange Point, to ensure that medication possibly dispensed at other pharmacies was captured.[37]

Study variables and definitions

Study data included clinical characteristics (patient demographics, age at onset of asthma, smoking history, and atopic status), asthma control (assessed by the six-item Asthma Control Questionnaire [ACQ-6],[38] exacerbation rate, comorbidities (chronic rhinosinusitis with nasal polyps, gastroesophageal reflux disease, ABPA), inflammatory markers (leukocytes, eosinophils, neutrophils and total IgE in peripheral blood, and FeNO),[39] lung function measurements (prebronchodilator FEV_1 and FVC[40]), and data on treatment (receiving azithromycin or OCS maintenance treatment, OCS daily maintenance dose, and cumulative OCS dose).

Positive atopic status was defined as a score of greater than 0.35 kU/L for at least one of a set of specific aeroallergens tested. We also collected data on specific IgE for *Aspergillus fumigatus*. Blood tests for specific IgE for fungal agents other than *A fumigatus* are not part of the standard assessment in the Netherlands and therefore are unavailable in the registry.

Severe asthma exacerbations were defined by at least one of the following criteria: (1) the patient reported using OCS courses (if not receiving maintenance OCS), (2) the patient reported doubling the maintenance dose of OCS for at least 3 days, and (3) the patient reported unscheduled emergency visits or hospitalization for asthma. In RAPSODI, the number of exacerbations is categorically recorded. Therefore, the annualized exacerbation frequency was analyzed as the percentage of patients with an exacerbation frequency of none to one, two to five, or more than five exacerbations per year.

Daily maintenance OCS dose was defined as the prednisolone-equivalent daily maintenance dose of OCS (milligrams per day).

Cumulative OCS dose was calculated as the sum of the amount of issued tablets multiplied by the strength (milligrams per tablet) in months 12 to 0 and months 0 to 12.

Study outcomes

Primary outcomes. Co-primary study outcomes included (1) a change in categorized exacerbation frequency between 12 months before and 12 months after the start of anti-IL-5/5Ra therapy, and (2) a change in daily maintenance OCS dose (milligrams per day) after 12 months of therapy. In addition to the whole-group assessment, two subgroups were analyzed separately: patients who used maintenance OCS at anti-IL-5/5Ra initiation and those who did not.

Secondary outcomes. Secondary outcomes included the change in ACQ-6 and lung function parameters between baseline and 12 months after the initiation of anti-IL-5/5Ra therapy. In addition, we analyzed the change in cumulative OCS dose used 12 months before and 12 months after the start of anti-IL-5/5Ra therapy.

Statistical analysis

Patient and treatment characteristics are summarized using descriptive statistics. Continuous variables are expressed as mean (±SD) or median with interquartile range ([IQR], 25% to 75%). Differences in variables between 12 months before and 12 months after the initiation of anti-IL-5/5Ra therapy were analyzed using Wilcoxon signed-rank test or χ^2 test, when appropriate.

Because the results might be influenced by the concomitant presence of ABPA or by the effect of a non−IL-5/5Ra−targeted biologic treatment initiated within the follow-up year, we performed sensitivity analyses for the primary outcomes, first in the subgroup of patients after excluding those with known ABPA, and second after excluding patients who switched to a non−IL-5/5Ra−targeted biologic in the first year after anti-IL-5/5Ra initiation.

P less than .05 was considered statistically significant. All analyses were performed using SPSS software (version 24, IBM, Armonk, NY).

TABLE I. Baseline characteristics of patients with severe asthma and comorbid bronchiectasis

Patient characteristic	Total group (n = 97)
Age, y*	62 (54-68)
Male sex, n (%)	54 (55.7)
White race, n (%)	88 (91.7)
Never-smokers, n (%)	62 (63.9)
Pack-years, y*	13 (5-24)
Body mass index,* kg/m^2	26.2 (23.3-28.8)
Age at asthma onset, y*	43 (18-59)
Atopic asthma, n (%)	44 (45.4)
Asthma Control Questionnaire results*	2.33 (1.50-3.0)
Exacerbation frequency, n (%)	
0-1/y	24 (25.5)
2-5/y	48 (51.1)
>5/y	22 (23.4)
Pulmonary function	
Pre-BD FEV1 (% predicted)*	72 (56-90)
FEV1/FVC ratio (%)*	63 (55-73)
Surrogate inflammatory parameters	
Blood eosinophils (×109 cells/L)*	0.38 (0.20-0.63)
Highest blood eosinophils ever (×109 cells/L)*	0.70 (0.47-1.20)
Total IgE, IU/mL*	151 (55-358)
FeNO (parts per billion)*	43.5 (19.5-75)
Blood leukocytes (×109 cells/L)*	8.65 (7.40-11)
Blood neutrophils (×109 cells/L)*	5.63 (3.84-7.69)
Comorbidity†	
Allergic bronchopulmonary aspergillosis, n (%)	8 (8.2)
Chronic rhinosinusitis with nasal polyps, n (%)	55 (56.7)
Gastroesophageal reflux, n (%)	13 (13.4)
Treatment	
Oral corticosteroid maintenance therapy, n (%)	45 (47.4)
Treatment with maintenance azithromycin, n (%)	21 (21.6)

BD, bronchodilator.
Data are presented as n (%) or mean ± SD or unless otherwise stated.
*Median (interquartile range).
†Physician reported comorbidity.

RESULTS

Patients

Of 1,023 patients with severe asthma included in the RAPSODI registry on September 1, 2021, 161 patients had comorbid bronchiectasis (16%), 97 of whom had initiated anti-

TABLE II. Effect of anti-IL-5/5Ra therapy on exacerbation frequency and OCS dose in patients with severe asthma and comorbid bronchiectasis (n = 97)

	At baseline (anti-IL-5/5R initiation)	At 12-mo follow-up	*P*
Exacerbation frequency, n (%)			< .001
0-1/y	24 (25.5)	74 (77.9)	
2-5/y	48 (51.1)	21 (22.1)	
>5/y	22 (23.4)	0	
Missing, n	3	2	
OCS maintenance therapy,* n (%)	45 (47.4)	28 (29.5)	< .001
Daily OCS maintenance dose, mg/d†	10 (5-15)	2.5 (0-5.0)	< .001
OCS cumulative dose,‡ g/y†	1.61 (0.82-2.82)	0.51 (0.013-2.07)	<.001
OCS-dependent§ (n = 45)			
Exacerbation frequency, n (%)			< .001
0-1/y	15 (33.3)	31 (68.9)	
2-5/y	17 (37.8)	14 (31.1)	
>5/y	13 (28.9)	0	
Missing, n	0	0	
OCS maintenance therapy, n (%)	45 (100)	28 (30)	< .001
Daily OCS maintenance dose, mg/d†	10 (5-15)	2.5 (0-5.0)	< .001
OCS cumulative dose, g†	2.63 (1.74-3.69)	2.02 (0.81-2.70)	< .001
Non−OCS-dependent (n = 47)			
Exacerbation frequency, n (%)			< .001
0-1/y	8 (18.2)	40 (88.9)	
2-5/y	29 (65.9)	5 (11.1)	
>5/y	7 (15.9)	0	
Missing, n	3	2	
OCS cumulative dose, g†	1.0 (0.42-1.61)	0.067 (0-0.42)	< .001

OCS, oral corticosteroids.
*Valid n (five patients are missing data on OCS dependency).
†Data are presented as n (%) or median (interquartile range).
‡Cumulative OCS dose, calculated as the sum of the amount of issued tablets multiplied by the strength (milligrams per tablet) in during the preceding year and at 12 mo follow-up.
§OCS-dependent, defined as patients using maintenance OCS at anti-IL-5/5Ra initiation.

IL-5/5Ra biologics before September 1, 2020 with available follow-up data over a 12-month period (range, 11-16 months) (Figure 1).

Table I lists characteristics of the 97 included patients. Most patients were middle-aged, had adult-onset asthma, and were nonatopic. The majority of patients had two or more exacerbations per year, about half of them received maintenance OCS, and 21% of patients were treated with maintenance azithromycin. Whereas nasal polyposis was present in more than half of patients, only 8% received the diagnosis of ABPA.

Effect of anti-IL-5/5Ra therapy on exacerbation rate and OCS dose

Exacerbation frequency. Within the total population, 75% of patients had two or more exacerbations in the year before anti-IL-5/5Ra biologic initiation, which decreased to 22% in the year after starting biologic therapy ($P < .001$). This beneficial effect was seen in both OCS-dependent and non−OCS dependent patients (Table II and Figure 2).

Oral corticosteroid use. Within the total population of patients with severe eosinophilic asthma and bronchiectasis, 47.4% were receiving maintenance OCS before initiating anti-IL-5/5Ra therapy, which decreased to 29.5% after 12 months of follow-up ($P < .001$) (Table II). In the OCS-dependent patients (n = 45), the daily maintenance OCS dose decreased from a median (IQR) of 10.0 (5-15) mg/d to 2.5 (0-5) mg/d after 12 months ($P < .001$). Of 45 patients with maintenance OCS at baseline, 35 (78%) showed a 50% or greater reduction in daily maintenance OCS dose after 1 year of anti-IL-5/5Ra therapy. Figure 3 and Table II show the cumulative OCS dose for 12 months before and 12 months after starting anti-IL-5/5Ra therapy; it was significantly reduced for the total population and both subgroups.

Similar significant effects in primary outcomes were found (see Sensitivity Analysis in this article's Online Repository at www.jaci-inpractice.org) when we excluded patients with comorbid ABPA (n = 8) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) or those who switched to a non−IL-5/5Ra−targeted biologic (n = 2) (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Effect of anti-IL-5/5Ra therapy on asthma control and lung function

Asthma control as assessed by ACQ-6 score significantly improved from 2.33 (1.50-3.0) at the start of biologic therapy to 1.29 (0.57-2.0) after 12 months of treatment ($P < .001$).

After 12 months of anti-IL-5/5Ra therapy, median (IQR) FEV1 nonsignificantly ($P = .13$) increased from 72 (56-90) percent predicted to 77 (61-94) percent predicted. Moreover,

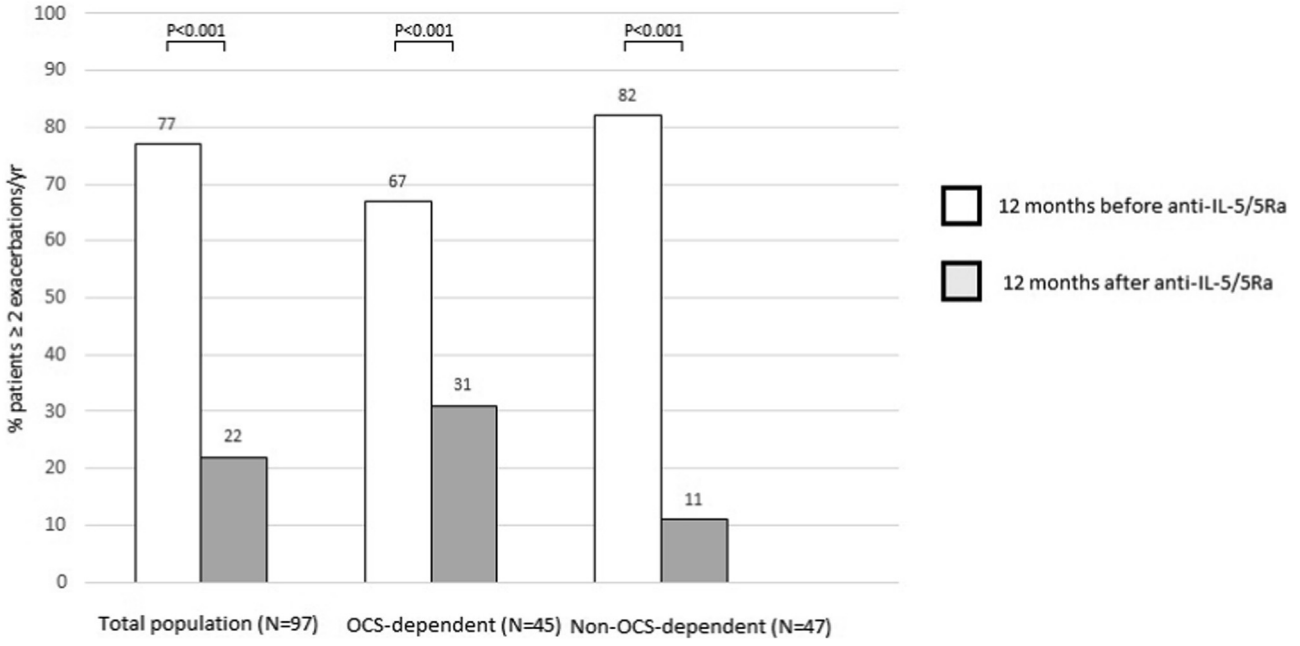

FIGURE 2. Effect of anti-IL-5/5Ra therapy on severe asthma exacerbations from12 months before to 12 months after initiation. *OCS*, oral corticosteroids. Valid n (five patients were missing data for OCS dependency).

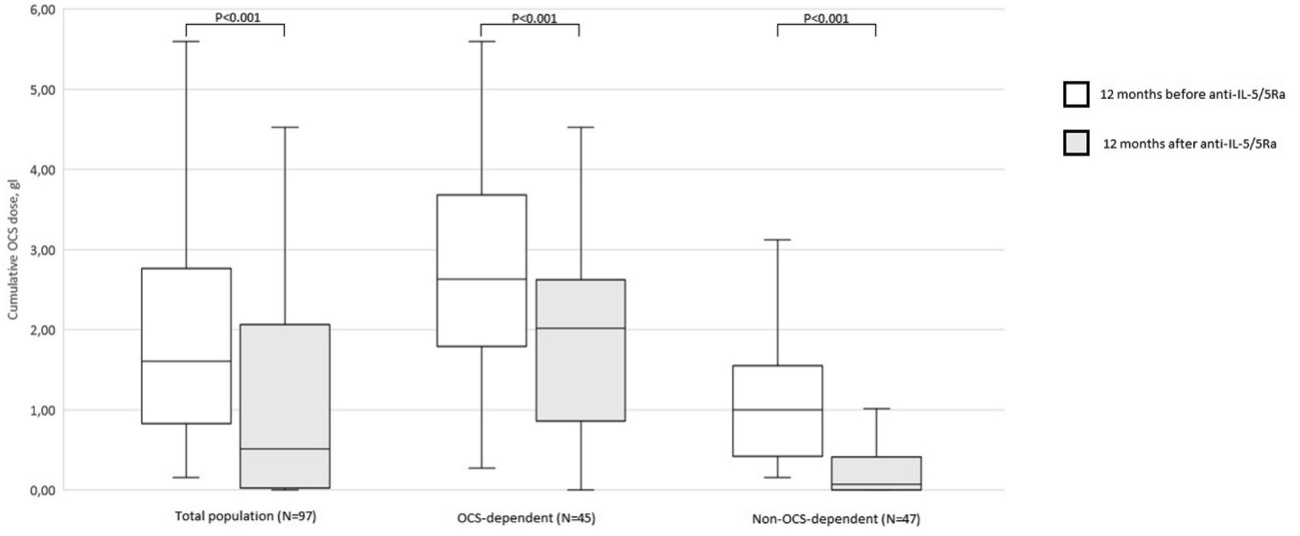

FIGURE 3. Cumulative oral corticosteroids (OCS) dose from 12 months before to 12 months after initiation of anti-IL-5/5Ra therapy. Valid n (five patients were missing data for OCS dependency).

there was no significant change in FVC percent predicted and FEV_1/FVC 1 year after the start of anti-IL-5/5Ra therapy.

DISCUSSION

This real-world study shows that treatment with IL-5/5Ra—targeted biologics reduces exacerbation frequency and OCS use in patients with severe eosinophilic asthma and comorbid bronchiectasis. This applies to patients who did not use OCS daily, as well as patients on maintenance treatment with OCS, despite tapering the daily OCS dose in the majority of the latter patients. In addition, an important and clinically relevant improvement in ACQ-6 score was seen after 12 months of treatment with anti-IL-5/5Ra therapy, similar to results in previous phase 3 studies in severe asthma patients without comorbid bronchiectasis.[20,21] These results suggest that anti-IL-5/5Ra biologics should be considered as add-on therapy for patients with severe eosinophilic asthma and comorbid bronchiectasis. The demonstrated OCS-sparing effect may be particularly relevant in this patient group.

This is the first nationwide study evaluating the real-life response to anti-IL-5/5R therapy in a large cohort of patients with severe eosinophilic asthma and concomitant bronchiectasis. Because comorbid bronchiectasis was an exclusion criteria in phase 3 trials, evidence is scarce regarding the effectiveness of IL-5/5Ra–targeted biologics in this subset of patients with severe asthma. Two case series involving fewer than 10 patients with severe asthma and bronchiectasis reported significant improvements in the exacerbation rate and OCS use after 12 to 24 months of treatment with anti-IL-5/5Ra biologics.[29,30] Similar beneficial effects on the numbers of exacerbations and OCS dose were found in an Italian single-center study evaluating the effectiveness of mepolizumab in 16 patients with severe eosinophilic asthma patients who had bronchiectasis.[27] Our study in a larger cohort of patients with severe eosinophilic asthma and comorbid bronchiectasis confirms and extends these results by showing that anti-IL-5/5Ra biologics can significantly reduce frequent exacerbations and OCS exposure.

Our study had a number of important strengths, including the relatively large group of patients included and the nationwide, multicenter design that enhanced external validity. The large patient population allowed us to analyze patients separately with and without maintenance OCS use, mimicking the design of most phase 3 asthma trials on biologics. Moreover, our study provides good insight into the OCS-sparing effect of anti-IL-5/5Ra biologics in this population. We showed a reduction in patients who were dependent on daily OCS, accompanied by a lower median daily OCS dose. Moreover, we were able to demonstrate the significant effect on the cumulative OCS dose over the year, which is a better predictor of OCS-related side effects than the daily dose at some point in the disease,[17] and may be particularly relevant in this patient group.

Our study had some limitations as well. First, the diagnosis of bronchiectasis was based on information entered in the registry by the attending physician, and it cannot be excluded that a standardized CT scan performed in all patients, with an assessment by an independent radiologist, would have led to different numbers. By requiring positive answers to two questions that regarded bronchiectasis listed as a comorbidity as well as demonstrated on a CT scan, we made the chance of a false bronchiectasis label as small as possible, but we cannot fully exclude this possibility. Furthermore, our severe asthma registry provides no detailed information about the type, extent, and etiology of bronchiectasis, or the bronchiectasis severity index,[41] and sputum culture data are scarce. Therefore, we cannot analyze whether there is a relationship between these characteristics and the response to biologics. However, we found similar results when the analysis was repeated without the small group of patients with reported ABPA. Finally, as is the usual limitation inherent in the observational registry-based design of the study, we lacked a control group of patients with severe eosinophilic asthma and comorbid bronchiectasis who were not treated with anti-IL-5/5Ra, because patients without a biologic were less likely to be included in the registry. Aware of the reported effects in placebo arms of previous RCTs of biologics in severe asthma,[20-22] we realize the inherent risk of overestimating treatment effects in a study without a control group. We cannot exclude that other factors, such as improved compliance and inhalation technique, might also have influenced the better results, although in the Netherlands these factors need to be assessed and optimized in all patients before these patients are eligible for biologic therapy. Yet, even in the absence of such a control group, in our view, the degree of the observed effect justifies a recommendation to consider anti-IL-5/5Ra biologics as an add-on-therapy for patients with severe eosinophilic asthma and comorbid bronchiectasis.

The results of anti-IL-5/5Ra therapy in this population of patients with severe asthma and comorbid bronchiectasis are consistent with previous real-world studies evaluating the effectiveness of anti-IL-5/5Ra therapy in patients with severe eosinophilic asthma.[23,42] This suggests that there are no relevant differences in response to anti-IL-5/5Ra therapy between patients with and without comorbid bronchiectasis; however, future studies are needed to confirm this.

There is some evidence that patients with particularly severe asthma who have type 2 inflammation are likely to exhibit bronchiectasis.[6] A recent study suggested that type 2 inflammation can have a causative role in developing bronchiectasis.[43] Although the mechanism is not yet fully clarified, abundant eosinophilic bronchial inflammation and associated degranulation products are supposed to have a role in epithelial damage,[44] loss of the epithelial barrier, and consequently an increased susceptibility for upper and lower respiratory tract infections,[45,46] in addition to an impaired type 1 response to infections.[46] Future studies are needed to evaluate the long-term effect of type 2–directed biologics on modulating inflammatory and remodeling processes in patients with severe asthma who have bronchiectasis. In addition to IL5/5R–targeted biologics, it thus relevant to study the response to other biologics, such as anti-IL-4/R or antithymic stromal lymphopoietin, especially considering patients with mucus hypersecretion.

In addition to these research recommendations, our study has important clinical implications. The favorable response to 12-month anti-IL-5/5Ra therapy observed in this study indicates that physicians should not worry that the effect of IL5/5Ra–targeted biologics in patients with severe eosinophilic asthma and comorbid bronchiectasis will be below expectations, even though comorbid bronchiectasis was an exclusion criterion in the RCTs. Moreover, by demonstrating the effect on the cumulative OCS dose, we highlighted the significant OCS-sparing potential of IL5/5Ra–targeted biologics in these patients. This should further encourage physicians to consider these biologics in patients with severe asthma complicated by bronchiectasis, for whom reducing OCS exposure appears to be crucial in view of the suppression of immunity and risk for infections.

This study demonstrates that patients with severe eosinophilic asthma and comorbid bronchiectasis have an excellent response in terms of a reduction in exacerbation frequency and OCS use when treated with anti-IL-5/5Ra biologics in real life. Therefore, these patients with a substantial burden of disease should not be excluded from biologic therapy.

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Sensitivity analysis

Sensitivity analysis for primary outcomes were performed in the subgroup of patients (1) without allergic bronchopulmonary aspergillosis (n = 8) and (2) after excluding patients who switched to a non-IL-5/5Ra–targeted biologic in the first year after anti-IL-5/5Ra initiation (n = 2).

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TABLE E1. Effect of anti-IL-5/5Ra on exacerbation frequency and OCS dose in patients with severe asthma and comorbid bronchiectasis after excluding patients with ABPA

Patients (n = 73)*	At anti-IL-5/5Ra initiation	At 12-mo follow-up	*P*
Annualized exacerbation frequency, n (%)			< .001
0-1/y	19 (27.1)	58 (81.7)	
2-5/y	37 (52.9)	13 (18.3)	
>5/y	14 (20.0)	0	
Missing, n	3	2	
OCS maintenance therapy, n (%)	31 (42.5)	20 (27.4)	< .001
Daily OCS maintenance dose, mg/d†	10 (5-15)	5.0 (4.25-7.50)	< .001
OCS cumulative dose, g†	1.56 (0.82-2.76)	0.48 (0.00-2.12)	< .001

ABPA, allergic bronchopulmonary aspergillosis; *OCS*, oral corticosteroid.
Data are presented as n (%) except where specified.
*Valid n (missing value for 16 patients; no information on ABPA as comorbidity.
†Median (interquartile range).

TABLE E2. Effect of anti-IL-5/5Ra on exacerbation frequency and OCS dose in patients with severe asthma and comorbid bronchiectasis after excluding those who switched to a non–IL-5/5Ra–targeted biologic in first year after anti-IL-5/5Ra initiation

Patients (n = 95)	At anti-IL-5/5Ra initiation	At 12-mo follow-up	*P*
Annualized exacerbation rate, n (%)			< .001
0-1/y	24 (25.8)	72 (77.4)	
2-5/y	47 (50.5)	21 (22.6)	
>5/y	22 (23.7)	0	
Missing, n	2	2	
OCS maintenance therapy, n (%)	45 (47.4)	28 (29.5)	< .001
Daily OCS maintenance dose, mg/d*	10 (5-15)	5.0 (3.81-7.50)	< .001
OCS cumulative dose, g*	1.56 (0.82-2.85)	0.51 (0.07-2.07)	< .001

*Median (interquartile range).
OCS, oral corticosteroid.
Both patients who switched to a non–IL-5/5Ra–targeted biologic (n = 2) switched to anti-IL-4R.