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Original Article

Real-World Effectiveness of Reslizumab in Patients With Severe Eosinophilic Asthma – First Initiators and Switchers

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What is already known about this topic? Reslizumab, a biologic targeting IL-5, has been shown to reduce asthma exacerbations and have an oral corticosteroid-sparing effect in phase 3 and pre-post studies when given as add-on therapy to patients with severe eosinophilic asthma.

What does this article add to our knowledge? This real-world study confirmed the beneficial effects of reslizumab when given to patients as the first add-on treatment, but it also demonstrated additive effectiveness in patients switching from another type 2 biologic, which was confirmed by physicians.

How does this study impact current management guidelines? The results suggest that it may be worthwhile for clinicians to switch patients who do not respond adequately to a specific type 2 biologic to another add-on biologic, even if it targets the same molecular pathway.

BACKGROUND: Reslizumab, a biologic targeting IL-5, has been shown to reduce asthma exacerbations and maintenance oral corticosteroid use in randomized controlled trials and pre-post studies in patients with severe eosinophilic asthma. However, real-world effectiveness data of reslizumab are scarce, and it is unknown whether reslizumab has added value after switching from another type 2 biologic.

OBJECTIVE: To evaluate (1) the real-world effectiveness of reslizumab on severe asthma exacerbations, maintenance oral corticosteroid use, and overall treatment response, both in biologic-naive patients who initiated reslizumab and in those who switched from another type 2 biologic; and (2) physicians' experience with reslizumab treatment.

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Abbreviations used
ACQ- Asthma Control Questionnaire
BMI- Body mass index
eCRF- Electronic case report form
ICU- Intensive care unit
IQR- Interquartile range
OCS- Oral corticosteroids
OR- Odds ratio
RAPSODI- Dutch Registry of Adult Patients with Severe Asthma for Optimal Disease Management

METHODS: This observational real-world study evaluated data from 134 adults with severe eosinophilic asthma included in the Dutch severe asthma registry (RAPSODI), who initiated reslizumab treatment (4-weekly infusions, 0.3 mg/kg) before April 2020 and had follow-up data for 6 months and greater. Clinical asthma experts completed surveys on their experience with reslizumab treatment.

RESULTS: Overall, reslizumab reduced the exacerbation rate (odds ratio [95% CI] = 0.10 [0.05-0.21]; $P < .001$), oral corticosteroid use (OR [95% CI], 0.2 [0.0-0.5]; $P < .001$), and maintenance dose (median [CI], 5.0 [0.0-10.0] to 0.0 [0.0-5.0]; $P < .001$), with comparable results in biologic-naive reslizumab initiators and switchers. The overall response to reslizumab was graded good or excellent in 59.2% of patients. The additive effectiveness of reslizumab after switching from another biologic was reflected in physicians' surveys.

CONCLUSIONS: Real-world data show that reslizumab reduces severe asthma exacerbations and oral corticosteroid use in patients with severe eosinophilic asthma, both in biologic-naive reslizumab initiators and in those who switched from another type 2 biologic. This additional value of reslizumab was recognized by clinical asthma experts. **(J Allergy Clin Immunol Pract 2022;10:2099-108)**

Key words: *Asthma; Observational study; Registries; Biologic therapy; IL-5; Reslizumab; Clinical effectiveness; Glucocorticoids; Exacerbations; Survey*

INTRODUCTION

Severe asthma is a form of asthma that does not respond to the current inhaled preventer medication for asthma, or it responds insufficiently.[1,2] Patients with severe asthma face a sizeable daily disease burden with persistent symptoms of dyspnea, coughing, mucus production, and impaired daily life activity.[3,4] Moreover, these patients are at increased risk for severe, potentially fatal asthma exacerbations that can often be prevented only by frequent courses or the continuous use of oral corticosteroids (OCS), which are associated with serious long-term side effects.[5-7]

Most patients with severe refractory asthma exhibit type 2 airway inflammation with elevated eosinophils in sputum and blood.[8] For the add-on treatment of patients with this so-called "severe eosinophilic asthma," several biologics have become available in recent years targeting IL-5, a key cytokine responsible for the differentiation, maturation, recruitment, and activation of eosinophils.[9] In randomized clinical trials, these anti−IL-5 add-on treatments have been shown to reduce the rate of asthma exacerbations effectively, lower the dose of maintenance OCS, and improve asthma symptoms, pulmonary function, and quality of life in patients with severe eosinophilic asthma.[10,11]

One such add-on treatment is reslizumab, an IgG subclass 4κ monoclonal antibody targeting IL-5 and given intravenously to patients with severe eosinophilic asthma and blood eosinophils of 400 cells/μL or greater.[12] The efficacy of reslizumab has been convincingly demonstrated in prospective, randomized clinical trials, but data on the real-life effectiveness of this antibody outside clinical trials are scarce.[13-17] In real-life, patients receiving asthma biologics often switch among currently available ones, but it is unclear why physicians decide to switch, or whether switching between biologics has any additional value.[18]

In this study, we evaluated the real-world effectiveness of reslizumab on severe asthma exacerbations, maintenance OCS users, and maintenance OCS dose and the overall quality of treatment response, in both patients who initiated reslizumab as the first asthma biologic and those who had switched from another type 2 biologic. We also evaluated physicians' expectations and clinical experience with reslizumab treatment. For the analyses, we used real-world longitudinal patient-level data from RAPSODI, the Dutch Registry of Adult Patients with Severe Asthma for Optimal Disease Management,[19] and an anonymized online survey distributed among all Dutch physicians who had treated RAPSODI patients with reslizumab.

METHODS

Study population

The study population consisted of all adult patients with severe asthma included in RAPSODI who initiated reslizumab between

sponsored by Health Holland involving many private partners that contribute in cash and/or in kind (Boehringer Ingelheim, Breathomix, Fluidda, Ortec Logiqcare, Philips, Quantib-U, Smartfish, SODAQ, Thirona, TopMD, and Novartis); and she has served on advisory boards for AstraZeneca, GSK, and Boehringer Ingelheim with money paid to her institution. F.W.J.M. Smeenk reports that his department has received funds for lectures from AstraZeneca, TEVA, and Chiesi. M.J.T. van de Ven participated in the advisory board from GSK, AstraZeneca, and Chiesi (2020/2021). E.J.M. Weersink reports grants from Novartis, GSK, and Sanofi-Genzyme outside the submitted work. A. ten Brinke reports institutional grants from GSK, TEVA, and Astra Zeneca outside the submitted work and participated in advisory boards for AstraZeneca, TEVA, and Sanofi-Genzyme Regeneron. J.K. Sont reports institutional research grant from AstraZeneca NL outside the submitted work. E.H Bel reports institutional grants from GSK and Teva and personal fees from AstraZeneca, GSK, Sanofi-Genzyme Regeneron, Chiesi, Sterna, and Teva outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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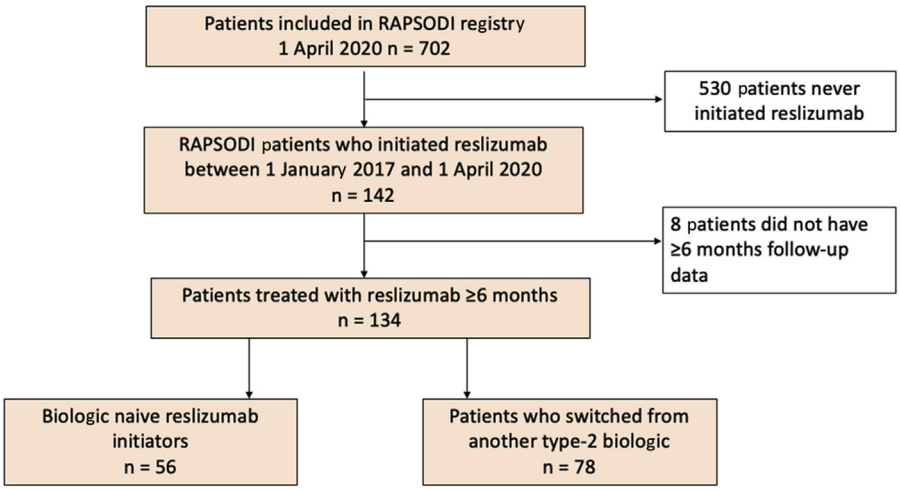

FIGURE 1. Biologic-naive reslizumab initiators were patients who started reslizumab treatment as the first add-on biologic. Patients who switched from another type 2 biologic were patients who started reslizumab treatment after ceasing another type 2 biologic. *RAPSODI*, Dutch Registry of Adult Patients with Severe Asthma for Optimal Disease Management.

TABLE I. Quality of response to reslizumab*

Category	Definition
Excellent response	None to one asthma exacerbations within 6 mo after reslizumab initiation AND No maintenance OCS at 6 mo after reslizumab initiation
Good response	Ineligible for category 1 (excellent response) No to one asthma exacerbations within 6 mo after reslizumab initiation AND ≥50% reduction in average maintenance OCS dose (mg/d) at 6 mo after reslizumab initiation
Partial response	Ineligible for categories 1 or 2 (excellent response or good response) AND Two to five asthma exacerbations within 6 mo after reslizumab initiation OR Any reduction in average maintenance OCS dose (mg/d)
No response/treatment failure	Any of the following: More than five asthma exacerbations within 6 mo after reslizumab initiation OR No reduction in maintenance OCS dose (mg/d) OR Discontinuation owing to adverse events at any time

OCS, Oral corticosteroids.
*In the Dutch Registry of Adult Patients with Severe Asthma for Optimal Disease Management, exacerbation frequency was classified into three categories: no or one exacerbation, two to five exacerbations, and five or more exacerbations over the past year.

January 1, 2017 and April 1, 2020 and had follow-up data available at least 6 months after reslizumab initiation. We distinguished two groups of patients: biologic-naive reslizumab initiators (biologic-naive initiators) and patients who had switched from another type 2 biologic (switchers). Patients who participated in clinical trials at the time of reslizumab initiation were excluded. Figure 1 is a flowchart showing inclusion.

The Medical Ethics Review Committee of the Academic Medical Center was consulted before the execution of this study (Reference No. W21_075 #21.085).

Design

This was a multicenter, observational, registry-based study involving the extraction and analysis of data from RAPSODI. We first identified patients who had the first initiation with reslizumab before April 1, 2020. Then, we selected patients who had used reslizumab for 6 months or greater for the analysis. We used a pre-post approach (ie, patient characteristics and treatment outcomes at 6 months [ie, data collected at a time point closest to 6 months or greater] after reslizumab initiation were compared with data at the time of reslizumab initiation). If reslizumab treatment was preceded by another type 2 biologic, we also evaluated the effect of the first biologic by comparing data at the initiation of reslizumab with data at the initiation of the previous biologic. Before the results of this study were disclosed, a short anonymous survey was distributed to physicians who had treated RAPSODI patients with reslizumab about the clinical experience with this treatment.

Data source

We retrieved data from individuals with severe asthma from 19 Dutch hospitals from the RAPSODI registry, which is based on two sources: annual electronic case report forms (eCRFs) (CASTOR EDC platform, Amsterdam, The Netherlands),[20] and 3-monthly electronic patient questionnaires (PatientCoach, Leiden University Medical Center, Leiden, The Netherlands).[21] The eCRF included sections related to inclusion criteria for the study, demographics, asthma history, comorbidities, lung function, laboratory measures, and medication. At each center, designated staff contributed to registering data for eligible patients who provided written consent. The quality of data was assessed and any necessary follow-up with the centers was conducted. After data quality issues were resolved, data cleaning and preparation ensued, including identifying outlier

TABLE II. Patients' baseline characteristics

Characteristics	Observations	
Age, y (mean [range])	134	53.4 (21-83)
Female sex, n (%)	134	65 (48.5)
BMI, means (SD)	129	28.3 (5.9)
<25	43	22.8 (1.9)
25 ≤ BMI ≤ 30	45	27.4 (1.3)
>30	41	35.0 (4.9)
Onset of asthma age ≥18 y, n (%)	133	94 (70.7)
Smoking status, n (%)		
Never smoker	134	77 (57.5)
Former smoker		57 (42.5)
Current smoker		0
Pack-years, median (IQR)	127	0 (0-10)
High-dose inhaled corticosteroids	131	111 (84.7)
Long-acting β-agonist use	131	126 (96.1)
Long-acting muscarinic antagonist use	131	52 (39.6)
Antileukotriene use	130	22 (16.9)
OCS exposure		
Receiving OCS maintenance therapy, n (%)	133	77 (57.9)
OCS dose mg/d, median (IQR) (n = 77)	74	10 (5-15)
Exacerbations (annual rate), n (%)	131	
0-1		52 (39.6)
2-5		51 (38.9)
>5		28 (21.4)
Intensive care unit admission previous year, n (%)	132	4 (3.0)
Hospital admission previous 3 mo, n (%)	68	9 (13.2)
Unscheduled visits previous 3 mo, n (%)	68	
0		57 (83.8)
1		9 (13.2)
2		2 (2.9)
ACQ score, means (SD)	74	2.3 (1.2)
Well-controlled (ACQ ≤0.75)	74	6 (8.1)
Indeterminate (ACQ 0.76-1.49)		12 (16.2)
Not well-controlled (ACQ ≥1.50)		56 (75.7)
Asthma-Related Quality of Life Questionnaire score, means (SD)	73	4.9 (1.3)
Pulmonary function		
FEV_1 in mL, means (SD)	123	2452 (840)
FEV_1 %, means (SD)		76.1 (21.2)
FVC in mL, means (SD)	121	3910 (1,165)
FVC in %, means (SD)		97.8 (17.6)
FeNO in ppb, median (IQR)	107	35 (19-70)
Eosinophils, cells/μL, median (IQR)	120	305 (100-575)
IgE kU/L, median (IQR)	97	135 (64-375)
Positive allergen-specific IgE	82	43 (52.4)
Comorbidities	134	
Atopic dermatitis, n (%)		6 (4.5)
Allergic rhinoconjunctivitis, n (%)		14 (10.5)
Chronic rhinosinusitis, n (%)		51 (38.1)
Nasal polyposis, n (%)		37 (27.6)
Vocal cord dysfunction n (%)		3 (2.2)
Anxiety/depression, n (%)		14 (10.5)
Gastroesophageal reflux, n (%)		16 (11.9)
Chronic obstructive pulmonary disease, n (%)		0
Diabetes mellitus, n (%)		5 (3.7)
Chronic congestive heart failure, n (%)		1 (0.8)
Obstructive sleep apnea syndrome, n (%)		6 (4.5)
Obesity (BMI >30) n (%)		41 (30.5)
None of the above, n (%)		10 (7.5)
Biologics used before reslizumab	132	
Omalizumab, n (%)		3 (2.3)
Mepolizumab, n (%)		66 (50)
Benralizumab, n (%)		8 (6.1)
Dupilumab, n (%)		1 (0.76)
None		54 (40.1)

ACQ, Asthma Control Questionnaire; *BMI*, body mass index; *IQR*, interquartile range; *OCS*, oral corticosteroids.
For unscheduled emergency visits and hospital admissions, ACQ and Asthma-Related Quality of Life Questionnaire score data were missing because not all patients were able to enter data via the online platform PatientCoach. The definition for high-dose inhaled corticosteroids was ≥1,000 μg/d fluticasone dipropionate equivalent.

values, labeling and formatting variables, and creating new derived variables as required.

Patients included in RAPSODI were asked to complete two standard questionnaires every 3 months voluntarily: the Asthma Control Questionnaire (ACQ-6)[22] and the Asthma-Related Quality of Life Questionnaire,[23] as well as information about past asthma exacerbations through PatientCoach. Data from the PatientCoach platform were merged with data from Castor eCRF via the pseudonymized unique RAPSODI patient identifier.

For physicians' opinions about reslizumab add-on therapy, we used data from an anonymized survey completed by all physicians who had treated RAPSODI patients with reslizumab during the study period. The survey consisted of seven questions (see Physicians' Survey in this article's Online Repository at www.jaci-inpractice.org). Physicians were not aware of the study results at the time they completed the survey.

Study outcomes

Primary outcomes. Co-primary study outcomes included changes in the annualized exacerbation rate and changes in maintenance OCS dose (milligrams per day) after at least 6 months of reslizumab therapy for the whole group of reslizumab users.

Secondary outcomes. Secondary outcomes included changes in the proportion of patients using maintenance OCS after 6 months of reslizumab initiation, unscheduled emergency visits, hospitalizations, intensive care unit (ICU) admissions, and the overall quality of response to reslizumab.

Subgroup analyses. Two predefined subgroups were analyzed separately: biologic-naive reslizumab initiators (biologic naïve initiators), and patients who initiated reslizumab after having switched from another type 2 biologic (switchers).

Physicians' opinions. Physician's opinion about reslizumab add-on therapy included the degree of satisfaction with reslizumab given as first add-on biologic therapy or after switching from another type 2 biologic therapy. The physician's survey was written in

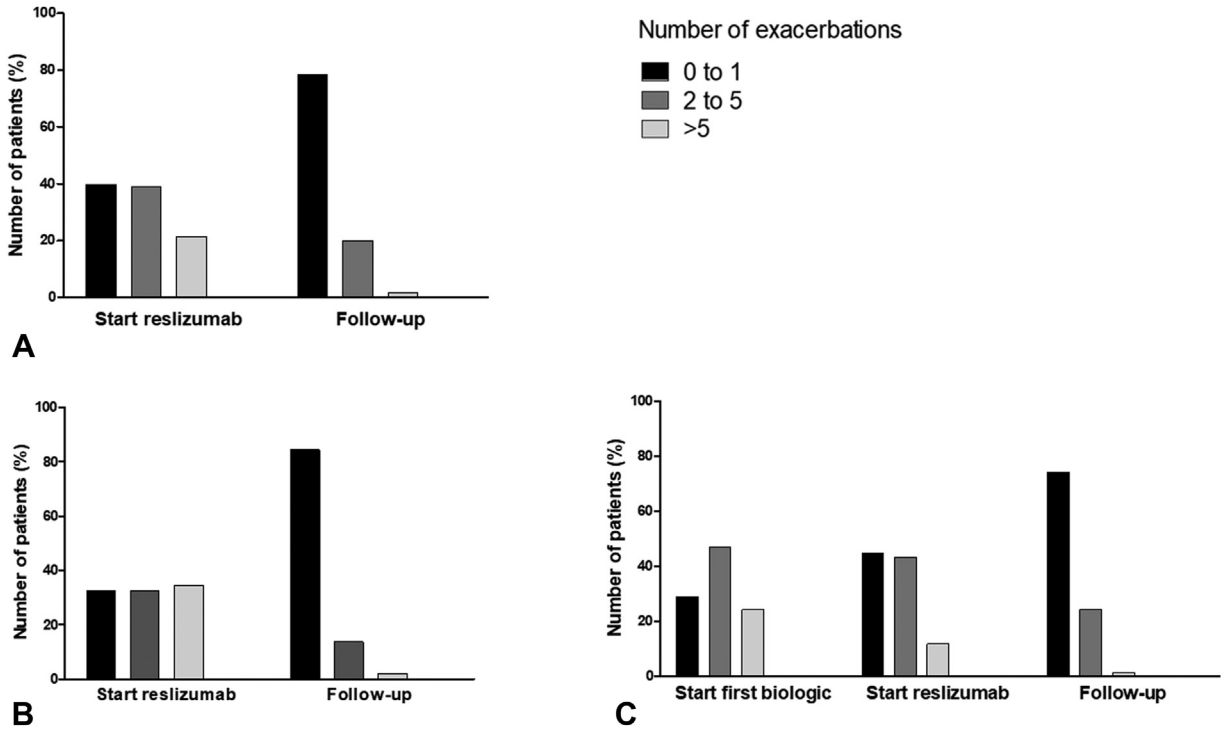

FIGURE 2. Effect of reslizumab on annualized exacerbation rate. The figure represents the proportion of patients experiencing none to one, two to five, or more than five severe asthma exacerbations in (**A**) all reslizumab users, (**B**) in the subgroup of patients who started with reslizumab as the first biologic (biologic-naive reslizumab initiators), and (**C**) in the subgroup of patients who started reslizumab after ceasing another type 2 biologic (switchers). Percentages are related to the number of patients in the same subgroup.

Dutch. An English translation and the complete results of the survey are available in the Online Repository.

Study variables and definitions

Study variables included demographics, questionnaire scores (ACQ and Asthma-Related Quality of Life Questionnaire), pulmonary function (FVC, FEV_1, comorbidities, inflammatory markers (blood eosinophils, FeNO, and total and specific IgE), exacerbation rate, asthma medication use, OCS use, OCS maintenance dose, and reasons for discontinuing reslizumab or switching from or to another biologic.

Severe asthma exacerbations were defined by at least one of the following criteria: (1) patient-reported use of OCS courses (if not receiving maintenance OCS); (2) patient-reported doubling of maintenance dose of OCS for at least 3 days; and (3) patient-reported unscheduled emergency visits or hospitalization for asthma.

Maintenance OCS dose before reslizumab initiation (or before initiating a previous biologic) was defined as the median daily dose of prednisolone equivalent (milligrams per day) within less than 1 month before initiation. Maintenance dose after reslizumab was defined as the daily dose of prednisolone equivalent collected at a point closest to 6 months or greater after reslizumab initiation.

Statistical analyses

Comparison of clinical outcomes before and after reslizumab initiation. Continuous variables are expressed as means with SDs or medians and interquartile range (IQR) (25% to 75%), where applicable. Categorical variables are expressed in absolute numbers and/or percentages.

We compared variables between pre-reslizumab initiation (start reslizumab) and after at least 6 months of reslizumab treatment (after 6 month or greater follow-up) and between preinitiation of another previous biologic treatment (start first biologic) and the switch to reslizumab treatment (switch to reslizumab). Comparisons of exacerbation rate categories, the proportion of OCS users, unscheduled emergency visits, hospitalizations, and ICU admissions were performed using mixed-effect (ordinal) logistic regression analysis employing all available data. Wilcoxon signed-paired analysis test was used for comparisons of OCS maintenance dose. P less than .05 was considered statistically significant (two-sided). We performed statistical analysis using Stata software (version 16, StataCorp LLC, College Station, Texas).

Estimation of proportion of patients who were reslizumab nonresponders. The number and proportion of reslizumab responders were calculated and categorized into mutually exclusive and exhaustive groups (Table I): (1) excellent response, (2) good response, (3) partial response, and (4) nonresponse or treatment failure. Counts and percentages were used to describe each component after reslizumab treatment initiation.

Physicians' survey. Counts and percentages were used to describe answers to each question on the survey.

RESULTS

Recruitment

Of 702 patients included in the RAPSODI registry on April 1, 2020, 142 had ever initiated reslizumab treatment between

TABLE III. Effect of reslizumab on exacerbation rate and OCS use

Outcomes	Start reslizumab	After ≥6 mo follow-up	*P*
Exacerbation annual rate			<.001
0-1	52 (39.6)	98 (78.4)	
2-5	51 (38.9)	25 (20.0)	
>5	28 (21.4)	2 (1.6)	
Missing, n	3	9	
OCS maintenance dose, mg/d			<.001
Median (95% CI)	5.0 (0-10.0)	0 (0-5.0)	
Missing, n	5	8	
Receiving OCS maintenance therapy (%)			<.001
Yes, n (%)	77 (57.9)	52 (39.7)	
No, n (%)	56 (42.1)	79 (60.3)	
Missing (n)	1	3	
Unscheduled visits previous 3 mo*			.05
0	57 (83.8)	72 (93.5)	
1-2	11 (16.2)	5 (6.5)	
Missing, n	66	57	
Patients hospitalized (previous 3 mo)*			NS
Yes, n (%)	9 (13.2)	7 (9.1)	
No, n (%)	59 (86.8)	70 (90.9)	
Missing, n	66	57	
Patients admitted to intensive care unit (previous year)			NS
Yes, n (%)	4 (3.0)	2 (1.5)	
No, n (%)	128 (97.0)	128 (98.5)	
Missing, n	2	4	

NS, Not significant; *OCS*, oral corticosteroids.
Comparisons of exacerbation rate categories, proportions of OCS users, unscheduled emergency visits, hospitalizations, and intensive care unit admissions were performed using mixed-effect (ordinal) logistic regression analysis using all available data. Wilcoxon signed-paired analysis test was used for comparisons of OCS maintenance dose.
*Only 74 of 134 patients filled out data in PatientCoach.

TABLE IV. Effect of reslizumab on primary outcomes in biologic-naive reslizumab initiators (n = 56)

Outcomes	Start reslizumab	After 6 mo follow-up	*P*
Exacerbation annual rate			<.001
0-1, n (%)	18 (32.7)	43 (84.3)	
2-5, n (%)	18 (32.7)	7 (13.7)	
>5, n (%)	19 (34.6)	1 (2.0)	
Missing, n (%)	1	5	
OCS maintenance dose, mg/d			.02
Median (95% CI)	0 (0-10.0)	0 (0-5.0)	
Missing, n	1	4	
Receiving OCS maintenance therapy			.09
Yes, n (%)	27 (48.2)	19 (35.2)	
No, n (%)	29 (51.8)	35 (64.8)	
Missing, n	0	2	
Unscheduled visits previous 3 mo*			NS
0	27 (90.0)	35 (97.2)	
1-2	3 (10.0)	1 (2.7)	
Missing, n	26	20	
Patients hospitalized (previous 3 mo)*			NS
Yes, n (%)	3 (10)	3 (8.3)	
No, n (%)	27 (90)	33 (91.7)	
Missing, n	26	20	
Patients admitted to intensive care unit (previous year)			NS
Yes, n (%)	2 (3.6)	1 (1.9)	
No, n (%)	54 (96.4)	52 (98.1)	
Missing, n	0	3	

NS, Not significant; *OCS*, oral corticosteroids.
Comparisons of exacerbation rate categories, proportion of OCS users, unscheduled emergency visits, hospitalizations, and intensive care unit admissions were performed using mixed-effect (ordinal) logistic regression analysis using all available data. Wilcoxon signed-paired analysis test was used for comparisons of OCS maintenance dose.
*Only 34 of 56 patients filled out data in PatientCoach.

January 1, 2017 and April 1, 2020. Eight patients (6%) did not fulfill inclusion criteria (ie, follow-up data less than 6 months).

Baseline characteristics

Table II lists baseline characteristics of 134 included patients at reslizumab initiation. Of note, 57.9% of reslizumab initiators used OCS daily, 60% had used another type 2 biologic before reslizumab, 70.7% had adult-onset asthma, 42.5% were former smokers, and 92.5% had at least one comorbidity.

Effect of reslizumab on exacerbation rate and maintenance OCS dose

The median (IQR) follow-up after reslizumab initiation was 12 months (12-14 months) for all reslizumab initiators (n = 134), 12 months (12-12 months) for biologic-naive initiators (n = 56), and 12 months (12-15 months) for patients who had used another type 2 biologic before reslizumab (n = 78). This latter group had used the previous biologic type 2 treatment for at least 3 months (median, 9 [IQR, 5-17] months) and had discontinued treatment after a median (IQR) lag time of 1.6 (1-5) months before initiating reslizumab. In all reslizumab initiators (n = 134), reslizumab significantly reduced the annualized rate of exacerbations (odds ratio [OR] [95% CI] = 0.10 [0.05-0.21]; $P < .001$) (Figure 2, *A*), as well as the median (95% CI) maintenance dose of OCS from 5.0 (0.0-10.0) to 0 (0.0-5.0) mg/d ($P < .001$) (Table III). Significant effects in these variables were also observed in biologic-naive reslizumab initiators (Table IV, Figure 2, *B*) and those who had switched from another biologic (Table V, Figure 2, *C*).

Effect of reslizumab on OCS users, emergency visits, hospitalizations, and ICU admissions

In all reslizumab initiators (n = 134), the proportion of OCS users decreased from 57.9% to 39.7% (OR [95% CI] = 0.20 [0.08-0.48]; $P < .001$) (Table III). In biologic-naive reslizumab initiators (n = 56), it decreased from 48.2% to 35.2% (0.11 [0.01-1.45]; $P = .09$) (Table IV), and in switchers from another

TABLE V. Effect of reslizumab on primary outcomes in patients who had switched from another type 2 biologic (n = 78)

Outcomes	Start first biologic (B1)	Switch to reslizumab (B2)	6-mo follow-up (FU)	*P* (B2-B1)	*P* (FU-B2)
Exacerbation annual rate				<.01	<.001
0-1, n (%)	19 (28.8)	34 (44.7)	55 (74.3)		
2-5, n (%)	31 (47.0)	33 (43.4)	18 (24.3)		
>5, n (%)	16 (24.2)	9 (11.8)	1 (1.3)		
Missing, n (%)	12	2	4		
OCS maintenance dose, mg/d				.03	<.01
Median (95% CI)	10 (0-15.0)	5.0 (0-0.0)	0 (0-5.5)		
Missing, n	19	4	4		
Receiving OCS maintenance therapy				.04	<.01
Yes, n (%)	54 (76.1)	50 (64.9)	33 (42.9)		
No, n (%)	17 (23.9)	27 (35.1)	44 (57.1)		
Missing, n	7	1	1		
Unscheduled visits previous 3 mo*				NS	.07
0	17 (77.2)	30 (78.9)	37 (90.2)		
1-2	5 (22.7)	8 (21.1)	4 (9.8)		
Missing, n	56	40	37		
Patients hospitalized (previous 3 mo)*				NS	NS
Yes, n (%)	2 (9.1)	6 (15.8)	4 (9.8)		
No, n (%)	20 (90.9)	32 (84.2)	37 (90.2)		
Missing, n	56	40	37		
Patients admitted to intensive care unit (previous year)				NS	NS
Yes, n (%)	7 (9.5)	2 (2.6)	1 (1.3)		
No, n (%)	67 (90.5)	74 (97.3)	76 (98.7)		
Missing, n	4	2	1		

NS, Not significant; *OCS*, oral corticosteroids.
Comparisons of exacerbation rate categories, proportions of OCS users, unscheduled emergency visits, hospitalizations, and intensive care unit admissions were performed using mixed-effect (ordinal) logistic regression analysis using all available data. Wilcoxon signed-paired analysis test was used for comparisons of OCS maintenance dose.
*Only 48 of 78 patients filled out data in PatientCoach.

TABLE VI. Effect of reslizumab on quality of treatment response after ≥6 mo

Treatment response	All patients	Biologic-naive initiators	Switchers
n	134	56	78
Excellent, n (%)	65 (52.0)	31 (59.6)	34 (46.6)
Good, n (%)	9 (7.2)	5 (9.6)	4 (5.5)
Partial, n (%)	34 (27.2)	11 (21.2)	23 (31.5)
No response, n (%)	17 (13.6)	5 (9.6)	12 (16.4)
Missing, n	9	4	5

OCS, Oral corticosteroids. Excellent response: no or one clinical asthma exacerbations after reslizumab initiation AND no maintenance OCS; good response: ineligible for category of excellent response AND no or one clinical asthma exacerbations AND ≥50% reduction maintenance OCS; partial response: ineligible for category of excellent response or good response AND two to five clinical asthma exacerbations OR any reduction OCS dose; no response: more than five clinical asthma exacerbations OR treatment discontinuation owing to adverse events OR no reduction in OCS dose.

type 2 biologic (n = 78), it decreased from 64.9% to 42.9% (0.23 [0.08-0.60]; $P = .003$) (Table V).

Unscheduled emergency visits and hospitalizations could be analyzed only in patients who filled out the online questionnaires (n = 74). These patients appeared to have milder disease given the lower OCS maintenance dose, the lower exacerbation rate, and the lower blood eosinophil count at reslizumab initiation (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

In these 74 patients, the proportion with one or more unscheduled emergency visit decreased from 16.2% to 6.5% (OR [95% CI] = 0.06 (0.00-0.96); $P = .05$) (Table III). Numbers of hospitalizations and ICU admissions were too small for reliable analyses. This was also true for secondary outcomes in the subgroups (Tables IV and V).

Effect of reslizumab on quality of treatment response

Table VI and Figure 3 summarize the effect of reslizumab on the quality of treatment response to reslizumab in all patients, biologic-naive reslizumab initiators and switchers. Among biologic-naïve initiators, 69.2% of patients showed a good or excellent response and 9.6% did not improve. In patients who had switched from another type 2 biologic, 52.1% showed a good or excellent response and 16.4% showed no response. A comparison of treatment responses between the subgroups showed a trend toward a worse response in switchers compared with biologic-naive initiators (OR [95% CI] = 0.55 [0.28-1.09]; $p = .09$).

Results from physician's survey on reslizumab therapy

The survey responses are illustrated in Figure 4, *A* and Figure 4, *B* and Figures E1-7 (in this article's Online Repository at www.jaci-inpractice.org). Ten of 13 physicians prescribing reslizumab as one of five available type 2 add-on biologics for

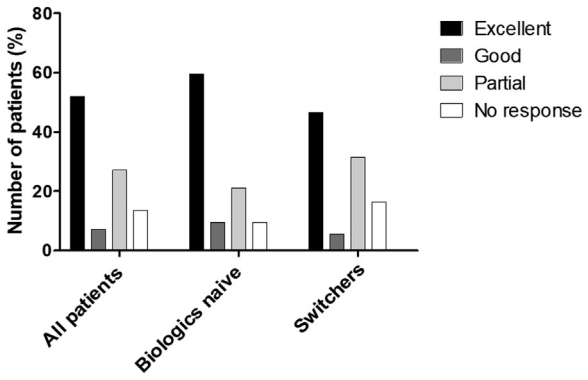

FIGURE 3. Effect of reslizumab on quality of treatment response after 6 months or more. The figure represents the response to reslizumab treatment after 6 months or more of follow-up in all reslizumab users (n = 134), in the subgroup of biologic-naive reslizumab initiators (patients who started with reslizumab as the first add-on biologic; n = 56), and in the subgroup of switchers (patients who started reslizumab after discontinuing another type 2 biologic; n = 78). Percentages relate to the number of patients in the same subgroup. Excellent response: no to one clinical asthma exacerbations after reslizumab initiation AND no maintenance OCS; good response: ineligible for category of excellent response AND no to one clinical asthma exacerbations AND 50% or more reduction maintenance OCS; partial response: ineligible for categories of excellent response or good response AND two to five clinical asthma exacerbations OR any reduction in OCS dose; no response: more than five clinical asthma exacerbations OR treatment discontinuation owing to adverse events OR no reduction in OCS dose.

RAPSODI patients responded to the survey. No physicians prescribed reslizumab solely as the first add-on treatment, 40% prescribed reslizumab solely as the second or third add-on biologic, and 60% prescribed reslizumab as both the first and second or third add-on biologic (Figure E2). As a reason for prescribing reslizumab, 50% responded that they expected patients to respond better to reslizumab than to other type 2 biologics (Figure 4, *A* and E3). Moreover, 90% of physicians were satisfied or very satisfied with reslizumab (Figure E5) and 80% found reslizumab to be of added value over other biologics (Figure 4, *B* and E6).

DISCUSSION

This real-world study in patients with severe eosinophilic asthma shows that reslizumab add-on treatment significantly reduced the rate of asthma exacerbations, the proportion of patients receiving maintenance OCS, and the dose of maintenance OCS. These beneficial effects were evident not only in patients receiving reslizumab as the first add-on biologic therapy, but also in those who previously failed another type 2 biologic and switched to reslizumab. This additional beneficial effect of reslizumab over other type 2 biologics was confirmed by an anonymous survey among Dutch asthma experts treating patients with severe eosinophilic asthma. Included patients in this study were at the extreme end of asthma severity and complexity, because most (58%) were OCS-dependent and almost all (92%) had comorbidities. Yet, only a small minority of patients (13.6%) did not improve with this therapy.

This real-world study confirms and extends results from randomized controlled trials and pre-post studies in patients with eosinophilic asthma,[13,14] which showed that reslizumab reduces asthma exacerbations and OCS use and improves asthma control, lung function, and rescue medication use. Beneficial effects of reslizumab were also observed in two real-world studies. One such study reported results from 26 patients treated with reslizumab who were observed for 2 years.[16] The study showed sustained improvement in ACQ, a decrease in exacerbation rates, and a reduction in OCS maintenance dose from reslizumab therapy. Another real-world study conducted in the United States among 215 patients who initiated reslizumab showed a significant reduction in asthma symptoms, exacerbation rates, pulmonary function, and health care use after 6 months, in which half of OCS-dependent patients were able to eliminate OCS after 10 months.[17] Our study differs slightly from these studies because it included patients who received add-on therapy with reslizumab as the first type 2 biologic (biologic-naive patients) as well as patients who were previously treated with another type 2 biologic but had to discontinue treatment because of insufficient response or a serious adverse event. Remarkably, reslizumab treatment in the latter group showed an additional improvement in the rate of exacerbations and OCS use, which suggests that reslizumab offered added value over previous type 2 biologics, including those targeting IL-5 in half of patients.

Apart from the beneficial effects of reslizumab on the exacerbation rate and OCS use, our study had some noteworthy results. First, many patients included in this real-world study had characteristics that differed from those of patients in phase 3 trials, which would have precluded participation in these trials. For example, patients in our study may have had a history of heavy smoking, serious comorbidities such as cardiovascular diseases, maintenance OCS dosing above 30 mg/d, eosinophil counts of less than 400 cells/μL, or recent use of other type 2 biologics. Despite these differences in the asthma population, the beneficial effects of reslizumab in the real world were largely comparable to those of the phase 3 trials. This suggests that in the real-world, reslizumab is effective even if the strict inclusion criteria of phase 3 trials are not entirely met.

Another noteworthy finding of this study is that patients who were prescribed reslizumab in the real world appeared to have more severe asthma than those included in the phase 3 trials. For example, in our study, 48% of patients receiving reslizumab as the first add-on biologic therapy and 65% who used it as the second or third add-on biologic used daily maintenance OCS compared with only 12% and 19% in the two phase 3 trials.[13] Of the 78 patients who had switched from another asthma biologic before initiating reslizumab, only four (5%) had been able to stop OCS, whereas after switching to reslizumab, an additional 21 patients (27%) could completely eliminate OCS. Also, exacerbation rates and OCS maintenance dose were significantly further reduced after switching to reslizumab therapy. This suggests that switching from another asthma biologic to reslizumab, even when targeting the same cytokine, may be beneficial in some patients. Interestingly, this was also the opinion of 70% of asthma experts regarding the effectiveness of reslizumab compared with other type 2 biologics. However, no definitive judgment can be made regarding differences in effectiveness between asthma biologics until head-to-head trials have been conducted.

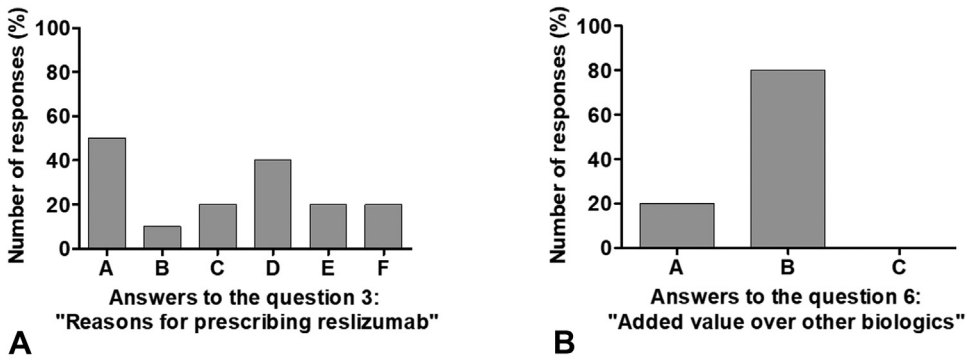

FIGURE 4. Physicians' experience with reslizumab use (anonymous survey). (**A**) Answers provided by doctors to the question "What were your reasons for prescribing reslizumab?" Multiple answers were possible: (A) Compared with other biologicals, I expected a greater effect on prednisone withdrawal and/or exacerbations; (B) Compared with other biologicals, I expected a greater effect on chronic sinusitis and nasal polyps; (C) Compared with other biologicals, I expected fewer side effects; (D) I found intravenous administration to be more reliable than subcutaneous administration; (E) I wanted to gain experience with this drug; (F) Other reason. (**B**) Answers provided by doctors to the question "Do you think reslizumab has any added value over other asthma biologics?" (A) No, not at all; (B): Yes, a little; (C) Yes, very much.

Our study showed that patients who initiated reslizumab as the first biologic had better overall outcomes at 6 months or greater compared with patients who had switched from another biologic. The most plausible explanation is that patients who switched were more likely to be OCS-dependent than were biologically naive patients, because of the higher percentage of patients receiving maintenance OCS at the time of starting reslizumab treatment as well as the higher median maintenance doses of OCS, whereas the number of exacerbations was lower (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Our study is unique in several respects. First, data in the multicenter Dutch RAPSODI registry are collected longitudinally in a standard way by both physicians and patients themselves, which makes this registry probably the best existing data source to conduct prospective real-world research on patients with severe asthma in The Netherlands. Second, we analyzed data from all 134 patients from this registry who had ever initiated reslizumab and were observed for at least 6 months before the beginning of the COVID-19 pandemic. Because more than half of these patients had received reslizumab as the second or third add-on asthma treatment, we were able to investigate whether switching from treatment with another asthma biologic to reslizumab would lead to further clinical improvement. Third, we added an anonymized physician survey to our study to verify whether asthma experts' real-world clinical experience with reslizumab was consistent with our study results. We considered this an important addition to a real-world study so that physicians' clinical impressions could be related to objective research data.

Our study also has several limitations that are inherent in the observational registry-based design of the study, such as the lack of a control group and possible hidden confounders. Furthermore, for patient-reported outcomes, many data were missing, which is unsurprising, because patients were asked to enter these data themselves voluntarily base via the PatientCoach platform. Therefore, although the numbers in the subgroups followed trends in the group as a whole, ultimately there were insufficient data to draw reliable conclusions regarding these patient-reported outcomes.

Both the findings of our study and the accompanying survey have clinical and research implications. The observed additional effect of reslizumab as a second or third add-on treatment suggests that it may be worthwhile to switch patients who do not respond adequately to one specific type 2 biologic to a second add-on biologic, even if this second biologic acts on the same molecular pathway. Further research will have to determine whether an improved response after switching from one anti-IL-5 biologic drug to another results from greater drug potency, better dosing, pharmacodynamics or pharmacokinetics, or the type of antibody or target, or whether it is merely a consequence of a longer-term inhibition of the inflammatory process in the airways with equally effective agents.

This study has shown that also in a real-world setting, reslizumab is effective in reducing exacerbations and OCS use in patients with severe eosinophilic asthma. When given after switching from another asthma biologic, even when it targets the same cytokine, reslizumab appears to produce additional clinical improvement, which is also recognized by asthma specialists according to an anonymous survey.

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ONLINE REPOSITORY

Physicians' Survey (English translation)

Dear colleagues,

This survey is an appendix to the soon-to-be published Dutch Registry of Adult Patients with Severe Asthma for Optimal Disease Management article "Real-world efficacy of reslizumab in severe asthma patients," written by Simone. The results of this (anonymous) survey will greatly increase the value of the manuscript. We hope for your cooperation.

Question 1: Have you ever prescribed reslizumab to your patients with severe asthma?

a) Yes: proceed to Question 2.
b) No: proceed to Question 9.

Question 2: For which indication have you prescribed reslizumab for your patients?

a) Only as first choice add-on biologic.
b) Only as second- or third-choice add-on biologic.
c) Both first- and second- or third-choice supplement biologics.

Question 3: What were your reasons for prescribing reslizumab? (Multiple answers possible)

a) Compared with other biologics, I expected a greater effect on prednisone withdrawal and/or exacerbations.
b) Compared with other biologics, I expected a greater effect on chronic sinusitis and nasal polyps.
c) Compared with other biologics, I expected fewer side effects.
d) I found intravenous administration to be more reliable than subcutaneous administration.
e) I wanted to gain experience with this drug.
f) Other reason.

Question 4: How satisfied were you with the overall effect of reslizumab as an add-on treatment?

a) Very dissatisfied
b) Dissatisfied
c) Neutral
d) Satisfied
e) Very satisfied

Question 5: How satisfied were or are your patients with reslizumab as an add-on treatment?

a) Very dissatisfied
b) Dissatisfied
c) Neutral
d) Satisfied
e) Very satisfied

Question 6: Do you think reslizumab has added value over other asthma biologics?

a) No, not at all
b) Yes, a little
c) Yes, very much

Question 7: Will you be prescribing more reslizumab in the future?

a) Yes, most likely. (End of survey)
b) No, most likely not

This is the end of the survey. Thank you for your cooperation!

TABLE E1. Patient characteristics of the whole group (n = 134) and of patients who entered data in PatientCoach (n = 74)

Characteristics	Whole group (n = 134)		PatientCoach (n = 74)	
Age, y (means [range])	134	53.4 (21-83)	74	53.7 (23-78)
Female sex, n (%)	134	65 (48.5)	74	36 (48.7)
Body mass index, means (SD) (n = 129)	129	28.3 (5.9)	74	29.2 (6.1)
Onset of asthma ≥18 y, n (%)	133	94 (70.7)	74	49 (66.2)
Smoking status, n (%)	134		74	
Never smoker		77 (57.5)		42 (56.8)
Former smoker		57 (42.5)		32 (43.2)
Current smoker		0		0
Pack-years, median (IQR)	127	0 (0-10)	70	0 (0-10)
Exacerbations (annual rate), n (%)	131		73	
0-1		52 (39.6)		27 (37.0)
2-5		51 (38.9)		28 (38.4)
≥5		28 (21.4)		18 (24.7)
Intensive care unit admission previous year, n (%)	132	4 (3.0)	74	3 (4.1)
Hospital admission previous 3 m, n (%)	68	9 (13.2)	66	8 (12.1)
Emergency room visits past 3 mo, n (%)	68		66	
0		57 (83.8)		55 (83.3)
1		9 (13.2)		9 (13.6)
2		2 (2.9)		2 (3.03)
ACQ score, means (SD)	74	2.3 (1.2)	74	2.8 (1.2)
Well-controlled (ACQ ≤0.75)	74	6 (8.1)	74	6 (8.1)
Indeterminate (ACQ 0.76-1.49)		12 (16.2)		12 (16.2)
Not well-controlled (ACQ ≥1.50)		56 (75.7)		56 (75.7)
Asthma-Related Quality of Life Questionnaire scores, means (SD)	73	4.9 (1.3)	71	4.8 (1.3)
Pulmonary function				
FEV_1 in mL, means (SD)	123	2452 (840)	71	2374 (830)
FEV_1 %, means (SD)		76.1 (21.2)		74 (21.8)
FVC in mL, means (SD)	121	3910 (1165)	70	3916 (1146)
FVC in %, means (SD)		97.8 (17.6)		97.9 (16.7)
FeNO in ppb, median (IQR)	107	35 (19-70)	63	31 (19-55)
Eosinophils, cells/μL, median (IQR)	120	305 (100-575)	72	250 (90-560)
IgE kU/L, median (IQR)	97	135 (64-375)	58	129 (64-366)
Positive allergen-specific IgE	82	43 (52.4)	45	24 (53.3)
Comorbidities	134		74	
Atopic dermatitis, n (%)		6 (4.5)		4 (5.4)
Allergic rhinoconjunctivitis, n (%)		14 (10.5)		10 (13.5)
Chronic rhinosinusitis, n (%)		51 (38.1)		31 (41.9)
Nasal polyposis, n (%)		37 (27.6)		22 (29.7)
Vocal cord dysfunction, n (%)		3 (2.2)		2 (2.7)
Anxiety/depression, n (%)		14 (10.5)		7 (9.5)
Gastroesophageal reflux, n (%)		16 (11.9)		10 (13.5)
Chronic obstructive pulmonary disease, n (%)		0		0
Diabetes mellitus, n (%)		5 (3.7)		3 (4.1)
Chronic congestive heart failure, n (%)		1 (0.8)		1 (1.4)
Obstructive sleep apnea syndrome, n (%)		6 (4.5)		4 (5.4)
Obesity n (%)		12 (9.0)		8 (10.8)
None of the above, n (%)		10 (7.5)		3 (4.1)
OCS exposure				
Receiving maintenance therapy, n (%)	133	77 (57.9)	74	39 (52.7)
Dose mg/d, median (IQR)	129	5 (0-10)	74	1.25 (0-10)
Biologics used before reslizumab	132		74	
Omalizumab, n (%)		3 (2.3)		2 (2.7)
Mepolizumab, n (%)		66 (50)		33 (44.6)
Benralizumab, n (%)		8 (6.1)		5 (6.7)
Dupilumab, n (%)		1 (0.76)		1 (1.4)
None, n (%)		54 (40.1)		33 (44.6)

ACQ, Asthma Control Questionnaire; *IQR*, interquartile range; *OCS*, oral corticosteroids.

TABLE E2. Baseline characteristics of biologic-naive reslizumab initiators and switchers

Characteristics	n	Naive initiators	n	Switchers
Age, y (mean [range])	56	53.9 (1.60)	78	52.8 (1.67)
Female sex, n (%)	56	29 (51.8)	78	36 (46.2)
BMI, mean (SD) (n = 129)	56	28.9 (0.75)	73	27.9 (0.71)
<25		15 (26.8)		28 (38.4)
25 ≤ BMI ≤ 30		17 (30.4)		28 (38.4)
>30		24 (42.8)		17 (23.2)
Onset of asthma ≥18 y, n (%)	56	38 (67.9)	78	56 72.7)
Smoking status, n (%)	56		78	
Never smoker		29 (51.8)		48 (61.5)
Former smoker		27 (48.2)		30 (38.5)
Current smoker		0		0
Pack-years, median (IQR)	56	0 (0-12)	78	0 (0-12)
High-dose inhaled corticosteroids	55	45	76	66
Long-acting β-agonist use	55	53	76	73
Long-acting muscarinic antagonist use	55	21	76	31
Antileukotriene use	55	11	75	11
Exacerbations (annual rate), n (%)	55		76	
0-1		18 (32.7)		34 (44.7)
2-5		18 (32.7)		33 (34.4)
>5		19 (34.6)		9 (11.8)
Intensive care unit admission previous year, n (%)	56	2 (3.57)	76	2 (2.63)
Hospital admission previous 3 mo, n (%)	56	3 (10)	76	6 (15.8)
Emergency room visits past 3 mo, n (%)	56		76	
0		27 (90)		30 (79.0)
1		3 (10)		6 (15.8)
2		0		2 (5.26)
ACQ score, mean (SD)	34	2.14 (0.19)	40	2.39 (0.21)
Well-controlled (ACQ ≤0.75)	34	2 (5.9)	40	4 (10)
Indeterminate (ACQ 0.76-1.49)		6 (17.7)		6 (15)
Not well-controlled (ACQ ≥1.50)		26 (76.5)		30 (75)
Asthma-Related Quality of Life scores, means (SD)	31	4.93 (0.21)	42	4.83 (0.15)
Pulmonary function				
FEV_1 in mL, means (SD)	55	2,486 (802)	68	2428 (874)
FEV_1 %, means (SD)		78.5 (21.2)		74.1 (21.11)
FVC in mL, means (SD)	54	3,998 (1179)	67	3,840 (1158)
FVC in %, means (SD)		101.2 (17.2)		95.0 (17.5)
FeNO in ppb, median (IQR)	50	30 (18-64)	57	42(26-80)
Eosinophils, cells/μL, median (IQR)	54	455 (250-620)	66	165 (40-400)
IgE kU/L, median (IQR)	53	135 (55-366)	44	130 (71-378)
Positive allergen-specific IgE, n (%)	47	25 (53)	35	18 (51%)
Comorbidities	56		78	
Atopic dermatitis, n (%)		6 (10.7)		6 (7.6)
Allergic rhinoconjunctivitis, n (%)		21 (37.5)		15 (19.2)
Chronic rhinosinusitis, n (%)		38 (67.8)		49 (62.8)
Nasal polyposis, n (%)		28 (50.0)		37 (47.4)
Vocal cord dysfunction, n (%)		1 (1.7)		1 (1.2)
Anxiety/depression, n (%)		6 (10.7)		14 (17.9)
Gastroesophageal reflux, n (%)		12 (21.4)		15 (19.2)
Chronic obstructive pulmonary disease, n (%)		0		0
Diabetes mellitus, n (%)		2 (3.5)		5 (6.4)
Chronic congestive heart failure, n (%)		1 (1.7)		0
Obstructive sleep apnea syndrome, n (%)		5 (8.9)		8 (10.2)
Obesity (BMI >30), n (%)		24 (42.8)		17 (23.2)
None of the above, n (%)		7 (12.5)		10 (12.8)

(continued)

TABLE E2. *(Continued)*

Characteristics	n	Naive initiators	n	Switchers
OCS exposure				
Receiving maintenance therapy, n (%)	56	27 (48.2)	77	50 (64.9)
Dose mg/d, median (IQR)	55	10 (5-10)	74	10 (5-15)

ACQ, Asthma control questionnaire; *BMI*, body mass index; *IQR*, interquartile range.
For unscheduled emergency visits, hospital admissions, ACQ, and Asthma-Related Quality of Life score data were missing because not all patients were able to enter data via the online platform (PatientCoach). The definition for high-dose inhaled corticosteroids was $\geq$1,000 μg/d fluticasone dipropionate equivalent.

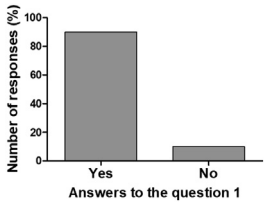

FIGURE E1. Answers provided by doctors to the question "Have you ever prescribed reslizumab (Cinqaero) to your patients with severe asthma?" A = yes; B = no.

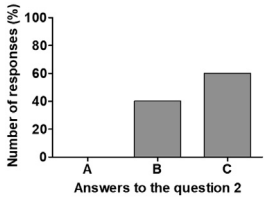

FIGURE E2. Answers provided by doctors to the question "For which indication have you prescribed reslizumab for your patients?" A: Only as first-choice add-on biologic. B: Only as second- or third-choice add-on biologic. C: Both first- and second- or third-choice supplement biologics.

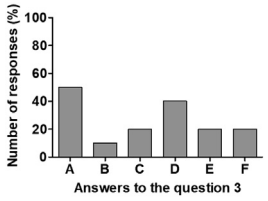

FIGURE E3. Answers provided by doctors to the question "What were your reasons for prescribing reslizumab?" Multiple answers were possible. A: Compared with other biologic, I expected a greater effect on prednisone withdrawal and/or exacerbations. B: Compared with other biologic, I expected a greater effect on chronic sinusitis and nasal polyps. C: Compared with other biologics, I expected fewer side effects. D: I found intravenous administration to be more reliable than subcutaneous administration. E: I wanted to gain experience with this drug. F: Other reason.

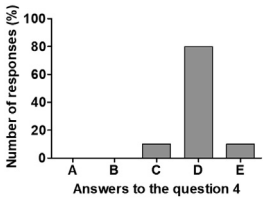

FIGURE E4. Answers provided by doctors to the question "How satisfied were you with the overall effect of reslizumab as an add-on treatment?" A: Very dissatisfied. B: Dissatisfied. C: Neutral. D: Satisfied. E: Very satisfied.

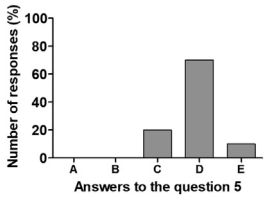

FIGURE E5. Answers provided by doctors to the question "How satisfied were or are your patients with reslizumab as an add-on treatment?" A: Very dissatisfied. B: Dissatisfied. C: Neutral. D: Satisfied. E: Very satisfied.

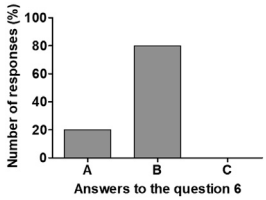

FIGURE E6. Answers provided by doctors to the question "Do you think reslizumab has added value over other asthma biologics?" A: No, not at all. B: Yes, a little. C: Yes, very much.

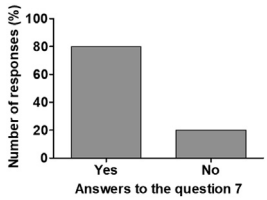

FIGURE E7. Answers provided by doctors to the question "Will you be prescribing more reslizumab in the future?" A: Yes, most likely. B: No, most likely not.