Early View

Original research article

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Johannes A. Kroes[1,2], Kim de Jong[3], Simone Hashimoto[4], Sander W. Zielhuis[1], Eric N van Roon[1,2], Jacob K. Sont[5], Anneke ten Brinke[6], on behalf of the RAPSODI team.

[1] Department of Clinical Pharmacy and Pharmacology, Medical Centre Leeuwarden, Leeuwarden, The Netherlands

[2] Unit of Pharmacotherapy, Epidemiology and Economics, Department of Pharmacy, University of Groningen, Groningen, The Netherlands

[3] Department of Epidemiology, Medical Centre Leeuwarden Academy, Leeuwarden, The Netherlands

[4] Department of Respiratory Medicine, Amsterdam University Medical Centres, University of Amsterdam, Amsterdam, The Netherlands

[5] Department of Biomedical Data Sciences, section Medical Decision Making, Leiden University Medical Centre, Leiden, The Netherlands

[6] Department of Pulmonology, Medical Centre Leeuwarden, Leeuwarden, The Netherlands

Corresponding author

Name: Johannes A Kroes

Address: Medical Centre Leeuwarden

                Dept. of Clinical Pharmacy and Pharmacology

                Henri Dunantweg 2

                8934 AD Leeuwarden

Phone: +3158 286 1837

Email: j.a.kroes@rug.nl

Take home message

Baseline characteristics and OCS dose and ACQ score at 3 months help predict long-term clinical response to benralizumab. Clinical tools, such as proposed in our study, could help clinicians predict future response to benralizumab.

Abstract

Background

Benralizumab is highly effective in many, but not all, patients with severe asthma. Baseline characteristics alone are insufficient to predict an individual's probability of long-term benralizumab response.

Objectives

To (1) study whether parameters at 3 months –in addition to baseline characteristics– contribute to the prediction of benralizumab response at 1 year and to (2) develop an easy-to-use prediction tool to assess an individual's probability of long-term response.

Methods

We assessed the effect of benralizumab treatment in 192 patients from the Dutch severe asthma registry (RAPSODI). To investigate predictors of long-term benralizumab response (≥50% reduction in maintenance oral corticosteroid (OCS) dose or annual exacerbation frequency) we used logistic regression, including baseline characteristics and 3-month Asthma Control Questionnaire (ACQ-6) score and maintenance OCS dose.

Results

Benralizumab treatment significantly improved several clinical outcomes and 144 (75%) patients were classified as long-term responders. Response prediction improved significantly when 3-month outcomes were added to a predictive model with baseline characteristics only (AUROC 0.85 vs 0.72, p=0.001). Based on this model, a prediction tool using gender, prior biologic use, baseline blood eosinophils, FEV_1 and at 3 months OCS dose and ACQ-6 was developed which classified patients into 3 categories with increasing probability of long-term response (95%CI): 25%(3-65), 67%(57-77) and 97%(91-99) respectively.

Conclusion

In addition to baseline characteristics, treatment outcomes at 3 months contribute to the prediction of benralizumab response at 1 year in patients with severe eosinophilic asthma. Prediction tools as proposed in this study may help physicians optimize the use of costly biologics.

Introduction

Severe eosinophilic asthma is associated with impaired quality of life, uncontrolled asthma symptoms,[1-4] and severe exacerbations that, until recently, could only be controlled by recurrent bursts or daily use of oral corticosteroids (OCS) putting patients at risk for serious long-term side effects.[5] This undesirable situation changed remarkably with the availability of biologics, especially biologics targeting Interleukin (IL)-5, a cytokine responsible for the recruitment and activation of eosinophils.[6]

One of these biologics is benralizumab, targeting the IL-5-receptor alpha subunit (IL-5Ra), which has been shown to be very effective in the treatment of severe eosinophilic asthma. In phase 3 randomized controlled trials (RCTs) benralizumab treatment has shown to induce a reduction in maintenance OCS dose and exacerbation frequency and an improvement in pulmonary function and patient-reported outcome measures (PROMs).[7-9] In addition, results of the recent open-label PONENTE study showed that the majority of patients initiating benralizumab were able to reduce or completely eliminate maintenance OCS.[10]

While benralizumab is highly effective in most patients, some patients have no response or only a partial response, resulting in discontinuation or switching to another biologic.[11-13] Given the high burden of disease and treatment costs, there is an urgent need for (bio)markers to predict long-term response to benralizumab.[14,15]

To date, a few studies have addressed the prediction of benralizumab response. Certain baseline characteristics, such as higher exacerbation frequency or higher blood eosinophil counts, are associated with more favorable benralizumab-induced outcomes, but it remains difficult to predict an individuals' probability of being a responder.[13,16] Next to baseline characteristics, early treatment effects may contribute to the prediction of long-term outcomes, as shown by a few studies that focused on predicting future asthma exacerbations or therapy response.[17-19] Whether the prediction of long-term response to benralizumab improves with the addition of early treatment outcomes to baseline characteristics is not yet known.

Therefore, we assessed the effects of benralizumab treatment using real-world patient data from the Dutch Severe Asthma Registry RAPSODI.[20] The primary aim of this study was to assess whether treatment outcomes at 3 months –in addition to baseline characteristics– contribute to the prediction of benralizumab response at 1 year. We further, exploratively, developed an easy-to-use prediction tool to enable clinicians to assess an individual patient's probability of long-term response to benralizumab treatment.

Methods

Study design and patient population

This was a nationwide, multicenter observational registry-based real-world population study. The study population consisted of patients with severe asthma included in the Dutch Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI). In RAPSODI, patient-level data is captured annually in a CASTOR EDC® eCRF from severe asthma patients in 19 Dutch hospitals. Furthermore, patients are asked to fill in 3-monthly electronic questionnaires (PatientCoach®, Leiden University Medical Center, Leiden, The Netherlands.[21]

All patients ≥18 years old who initiated benralizumab for severe eosinophilic asthma between 1 April 2018 and 1 October 2020 were included in this study. All patients were diagnosed with severe asthma according to the ERS/ATS guidelines.[22] Anti-IL-5Ra eligibility was based on blood eosinophils ≥0.3*10^9 cells/L or ≥0.15*10^9 cells/L for patients using OCS maintenance treatment.[23] Patients were excluded if they were lost to follow-up. Informed consent for this study was collected at registry-enrolment. For the current study, a formal approval from a medical ethics committee was waived according to Dutch legislation. The study was registered in the Netherlands Trial Register (registration number: NL8885).

Measurements

The Asthma Control Questionnaire (ACQ-6) at baseline, 3 months and 12 months after initiating benralizumab was collected using the application PatientCoach®. Other baseline characteristics at the moment of benralizumab initiation and clinical outcomes after 12 months were collected from the RAPSODI registry and included: patient demographics, asthma characteristics, medication (inhaled corticosteroids (ICS) dose, OCS use, OCS maintenance dose, previous biologic), exacerbation frequency in the 12 months before benralizumab initiation, lung function measurements (FEV_1), inflammatory markers (baseline peripheral blood eosinophils, fractional exhaled nitric oxide (FeNO)), and comorbidities (nasal polyposis, chronic rhinosinusitis, bronchiectasis). OCS maintenance dose

after 3 months of benralizumab treatment was collected from the patients' records. Clinical outcomes after 12 months were: continuation of benralizumab, exacerbation frequency in the previous 12 months, OCS use, OCS maintenance dose, ACQ-6, and FEV_1.

Study definitions

A positive response to benralizumab treatment was defined as continuation of benralizumab after 12 months and having a ≥50% reduction in annual exacerbation frequency or a ≥50% reduction in OCS maintenance dose. These patients were classified as responders. If benralizumab was discontinued at or before the 12 months mark or the patients did not achieve a ≥50% reduction in either OCS maintenance dose or exacerbations, the patients were classified as non-responders. Patients without maintenance OCS and exacerbations at baseline were excluded from the analysis. Asthma exacerbations were defined by at least one of the following criteria: 1) patient-reported use of OCS courses; 2) doubling of maintenance dose of OCS for at least 3 days; 3) unscheduled emergency visits or hospitalizations for asthma deterioration.

Statistical analysis

Assessment of clinical outcomes
Continuous variables are expressed as means (SD) or medians (IQR) whatever applicable and categorical variables as percentages. Baseline differences between responders and non-responders to benralizumab treatment were compared using t-tests and Mann-Whitney U-tests whatever applicable for continuous variables and Chi²-tests for categorical variables. Changes in clinical outcomes pre- and (3 or 12 months) post benralizumab initiation in the total group and within responder group were assessed using Wilcoxon signed-rank tests.

Predicting response
To investigate predictors of benralizumab response at 12 months, we used logistic regression, including commonly available baseline characteristics and clinical outcomes after 3 months as potential predictors. Variables with >20% missing data were considered not commonly available from clinical practice and were hence left out of the analysis. Variables univariately associated with

benralizumab response (P<0.20) were selected for multivariable logistic regression, following a full model approach in order to avoid predictor selection bias and overfitting.[25,26] Effect-sizes were expressed as odds ratios (OR) with 95% confidence intervals (95%CI). Discriminative ability was assessed with the area under the receiver-operating characteristic (AUROC) and calibration with the Hosmer-Lemeshow test and calibration plots. Based on AUROCs, a choice was made between incorporating either variables at baseline and 3 months or the change in these variables between baseline and 3 months. To assess the added value of the variables at 3 months in the prediction of long-term response, 2 multivariable models predicting long-term response were compared: a model with only baseline variables and a model with baseline variables combined with 3-months data. AUROCs of both regression models were compared using the DeLong-test.

Development of a prediction tool

Based on the univariately selected predictors, an easy-to-use tool was developed in order to predict an individual's probability of being a benralizumab responder. First, continuous variables were categorized according to clinically relevant cut-offs and a multivariable regression model was constructed. In order to construct a parsimonious model, variables that contributed marginally to the AUROC were excluded from the model. The model was internally validated and corrected for optimism using internal bootstrap resampling (1000 bootstrap samples).[27] Finally, score points were assigned to the variables based on the regression coefficients. Individual prediction scores were calculated to assess the performance of the model in the study population. Risk categories based on the absolute risk for response were established in order to make the model clinically applicable.

A P-value <0.05 indicated statistical significance. All statistical analyses were performed with IBM SPSS Statistics version 26.0 and STATA version 16.0.

Results

Patient characteristics at baseline

Two hundred twenty out of 814 patients included in the RAPSODI registry at 1st October 2020 initiated benralizumab between 1 April 2018 and 1 October 2020 (Figure 1). Twenty-eight patients (all switchers from another biologic) did not experience exacerbations in the year prior to benralizumab initiation and had no OCS maintenance treatment at baseline. These patients were unable to improve in exacerbations or OCS dose and were therefore left out of the analyses. Table 1 summarizes the characteristics of the study population at benralizumab initiation. Forty-eight percent of the participants were male, the majority of patients had adult-onset asthma, and almost half of the patients were previous smokers. Sixty-four percent of the patients received maintenance OCS when initiating benralizumab and 54.2% of them had previously used another biologic.

Fourty-four (22.9%) patients discontinued benralizumab within 12 months. The reasons for stopping were: failure to reduce symptoms (N=28), failure to reduce OCS (N=24), insufficient effect on pulmonary function (N=20), side effects (N=7), and other (N=2). Multiple reasons for discontinuing benralizumab were possible. No patients discontinued benralizumab solely based on insufficient effect on pulmonary function. The median (IQR) duration of treatment for patients discontinuing benralizumab was 4 (4-8) months. After discontinuing benralizumab, 22 patients completely ceased the use of biologics, 9 switched to another anti-IL-5 biologic and 13 patients switched to anti-IL-4/IL-13 treatment at the follow-up moment.

Real-world effectiveness of benralizumab

The effect of benralizumab treatment on several asthma-related outcomes is demonstrated in Figure 2 and Table 2. In the total population, initiating benralizumab led to a statistical significant improvement at 1 year of exacerbation frequency (median (IQR) 3 (2-5) exacerbations per year to 0 (0-1) exacerbations per year, p<0.01) and OCS maintenance dose (5 (0-10) mg/day to 0 (0-5) mg/day, p<0.01). In addition ACQ-6-score significantly improved from 2.17 (1.67-3.17) at baseline to 1.0 (0.5-

1.83) at 1 year, p<0.01, and FEV_1 (%predicted) from 72% (57-85) to 80% (66-96), p<0.01. A statistical significant improvement of OCS maintenance dose and ACQ-6-score was observed as early as 3 months after initiating benralizumab treatment.

One hundred fourty-four patients were classified as responders (continuing benralizumab after 12 months and have a ≥50% reduction in either exacerbation frequency or OCS maintenance dose). Fourty-eight patients discontinued benralizumab treatment or did not reduce exacerbation rate or OCS maintenance dose ≥50% and were labeled as non-responders.

Baseline characteristics of responders and non-responders are shown in Table 1. Responders differed from non-responders in that they were less likely to report the use of a prior biologic and were more often male. Responders tended to have higher levels of FeNO and blood eosinophil levels above 0.3×10^9 cells/L. Data on the effect of benralizumab on clinical outcomes for responders and non-responders are illustrated in Figure 2 and Table 2.

Predicting long-term benralizumab response

To explore whether 3 months data in addition to baseline characteristics can improve prediction of benralizumab response at 1 year, we used univariate logistic regression analyses (Table 3). Male gender, no previous biologic use, lower OCS dose at baseline, lower ACQ-6-score at baseline, higher FEV_1 at baseline, baseline blood eosinophils $\geq 0.3 \times 10^9$ cells/L, lower OCS dose at 3 months and lower ACQ-6 at 3 months were univariately associated with benralizumab response (P<0.20) and included in the multivariable analyses. 170 patients had complete data for all characteristics.

Table 4 demonstrates the multivariable logistic regression analyses of two models, the first model using only predictive parameters at baseline and the second model with predictors at baseline and 3 months. The model with only baseline predictors corresponded to an AUROC of 0.72 (95%CI 0.63-0.80), the Hosmer Lemeshow-test did not indicate bad fit (p=0.95). The model using baseline parameters combined with 3 months parameters corresponded to a higher AUROC than baseline predictors alone, namely 0.85 (95%CI 0.78-0.92). The Hosmer Lemeshow-test showed no indication of bad fit (p=0.41); for the calibration plots, see Supplementary Figure 1. The AUROCs of both

models were statistically significant different (p=0.001). Two exploratory analyses with only outcomes at 3 months and only the ACQ-6 at 3 months, are presented in the Supplementary Materials, Table S2. Both analyses yielded lower AUROCs than the model using baseline parameters combined with 3 months parameters.

Clinical assessment of long-term response

Based on the multivariable logistic regression model from Table 4, including both baseline and predictors at 3 months, we proposed an easy-to-use response prediction tool in Table 5 and Figure 3. Removal of the ACQ-6 at baseline and OCS dose at baseline had a minimal effect (-0.03) on the AUROC. Internal validation yielded a correction for optimism of 0.005 decrease in the AUROC. Three score categories for probability of long-term benralizumab response were established: low (score 0-2), intermediate (score 3-11) and high (score ≥12). Patients with a score ≥12 at 3 months had a very high probability (97%, 95%CI 91-99%) of benralizumab response after 12 months. The number of patients per score (0-19) and the proportion of patients and likelihood ratios per prediction category are described in Supplementary Table S1.

Discussion

The present study shows that treatment outcomes at 3 months –in addition to baseline characteristics– contribute to the prediction of benralizumab response at 1 year in patients with severe eosinophilic asthma. In this large nation-wide real-world population, benralizumab treatment significantly improved exacerbation frequency, OCS maintenance dose, ACQ-6 and FEV1. The majority (75%) of the 192 patients were responders to benralizumab treatment at 12 months. The prediction of response to benralizumab was significantly improved by adding two easy-to-assess parameters at 3 months (OCS dose and ACQ-6) to a set of baseline parameters, resulting in a predictive model with a higher AUROC and hence a higher discriminative capability. These results suggest that combining baseline data and short-term treatment outcomes and incorporating them into a simple tool, such as the one we propose, could help clinicians predict future response to benralizumab and thus promote the efficient use of costly biologics.

The beneficial effects of benralizumab, as well as its rapid onset, which we demonstrate in this study are in line with previous findings from randomized controlled trials and real-world studies.[7-10,19] However, in terms of response rate, we identified 25% non-responders, which is higher than the 13-14% reported in two UK studies.[12,19] This may be due to the higher number of patients with prior biologic use in our study but also the very strict eligibility criteria used in the UK and in these British studies which may have selected a more exacerbation-prone population resulting in lower rates of non-responders than experienced in other real-world settings.

The prediction of response to benralizumab has been studied before. Studies predicting response based on baseline characteristics found higher blood eosinophils, more frequent exacerbations, use of maintenance OCS, nasal polyposis, adult-onset asthma and higher levels of FEV_1 as important predictive parameters.[12,13,16,28] Early treatment outcomes as a parameter in predicting future response to benralizumab was studied in a single study in which an ACQ-6-improvement of ≥0.5 units 4 weeks after initiating benralizumab predicted response at 48 weeks.[19] Our study confirms and extends these findings, as we showed that a combination of baseline characteristics and early

treatment outcomes was most successful in identifying patients that are most likely to respond to benralizumab.

We found that 87.5% of biologic naïve patients were responders *vs.* 64.4% in patients with a previous biologic. No prior use of a biologic emerged as an important predictor of long-term response to benralizumab. In a recent study it was stated that benralizumab is effective in severe asthma independent of previous biologic use.[19] Also in the present population, patients with or without previous treatment with a biologic for severe asthma significantly benefited from benralizumab treatment (data not shown). However, the individual probability of responding to benralizumab treatment was significantly higher in patients without previous biologic use, justifying its inclusion in the predictive model.

A major strength of this study is that it analyzes the largest real-world population of benralizumab-treated patients, using the Dutch RAPSODI registry, which collects longitudinal data in a standardized way, both by clinicians and 3-monthly by patients themselves. This unique registry allowed us to include treatment outcomes at 3 months in the analysis of predictors of long-term response to benralizumab. This study also has limitations inherent to the real-world character and observational design of the study, such as lack of a control group and possible unnoticed confounders in the comparison of clinical outcomes. Further, incompleteness of some data meant that certain parameters, such as FeNO, could not be used in the prediction model. In addition, the blood eosinophils before initiating any biological treatment for the patients switching from another biologic or data on other comorbidities were not available. As limiting as this may seem, it reflects real-world practice and ultimately we are looking for predictive parameters that are easy to assess in every clinical practice and a prediction tool that is widely applicable, as presented in our study. We have optimized our predictive model through internal validation, but realize that external validation in another severe asthma population is required to confirm the applicability of our model and tool. Unfortunately, we do not have access to such an independent second population. Finally, we conducted our study at a time when the COVID-19 pandemic increasingly dominated the world. This

likely reduced both the rate of exacerbations and the willingness of clinicians or patients to discontinue or switch biologics and may therefore have resulted in fewer patients with non-response. Nevertheless, the number of non-responders in our study is still higher than observed in other studies[12,19], suggesting that the results were unlikely to have been significantly influenced in this regard, although we cannot exclude such an effect.

Our results have both clinical and research implications. We demonstrated a predictive model and developed a simple clinical scoring tool to help clinicians assess whether a patient is likely to respond to benralizumab treatment on the long-term. Where baseline characteristics alone are insufficient to predict an individual's probability of being a responder, our addition of parameters at 3 months succeeds in identifying patients with 97% probability on long-term benralizumab response. These patients may require less intensive monitoring, helping clinicians to allocate their valuable time. Further research will need to determine whether clinical tools integrating biomarkers, phenotypic features and clinical outcomes, such as the one proposed in our study, are a valuable addition to clinical practice, not only in predicting response to benralizumab or other biologics, but -even more challenging- in predicting non-response. The optimal set of variables to incorporate in these clinical tools might involve variables that were not available in our dataset, for example exacerbation frequency after 3 months. In addition, the best moment for response evaluation may differ between patients, as some patients may require more time to be labeled a responder. The optimal moment to evaluate treatment response needs to be elucidated. Evidence, such as provided in our manuscript, adds in this process.

In conclusion, this nationwide real-world study confirms the beneficial effects of benralizumab treatment on several clinical outcomes in patients with severe eosinophilic asthma. The prediction of long-term response to benralizumab was clearly improved by adding treatment outcomes at 3 months to baseline characteristics and long-term response could be determined using an easy-to-use scoring tool. Prediction tools, such as the one proposed in our study, are promising additions to

clinical practice, assisting clinicians in their clinical decision-making and further optimizing treatment with costly biologics.

Acknowledgements

Support statement

Conflict of interest statement

Tables

Table 1: Baseline characteristics for the total population, and stratified for non-responders and responders.

		Total population (N=192)	Non-responders (N=48)	Responders (N=144)	P-value
Age (y)*		58 (13)	58 (13)	58 (13)	0.99
Male gender (%)		48.4	37.5	52.1	0.080
Body mass index (kg/m²)*		28 (5.3)	28.7 (5.9)	27.7 (5.2)	0.26
Former smoker (%)		47.9	41.7	50.0	0.32
Pack years (y)† ˜		11 (5-22)	10 (5-30)	11 (6-22)	0.76
Age of asthma onset (y)*		41 (19)	37 (18)	42 (19)	0.25
Non atopic asthma (%)		65.2	64.4	65.5	0.90
Late asthma onset (%)		80.7	75	82.6	0.245
Exacerbation frequency last year (exacerbations per year)†		3 (2-5)	3 (2-4)	3 (2-5)	0.51
ICS daily dose (mg, fluticasone equivalents)†		1000 (750-1500)	1000 (800-1500)	1000 (750-1125)	0.38
OCS maintenance on baseline (%)		63.5	62.5	63.9	0.86
OCS dose baseline (mg/day)†‡		10 (5-15)	10 (7.5-20)	10 (5-13.8)	0.025
Previous biologic for severe asthma (%)		54.2	77.1	46.5	<0.001
Ever use of omalizumab (%)		14.1	22.9	11.1	
Ever use of mepolizumab (%)		43.8	56.3	39.6	
Ever use of reslizumab (%)		13	29.2	7.6	
Ever use of dupilumab (%)		2.1	2.1	2.1	
ACQ-6-score baseline†		2.17 (1.67-3.17)	2.5 (1.85-3.33)	2.17 (1.5-3.1)	0.054
FEV$_1$ prebronchodilator (%pred)*		71.5 (22.1)	67.2 (22.9)	72.9 (21.7)	0.13
FeNO (ppb)†		41 (22-73)	32 (16-60)	44 (25-74)	0.061
Blood eosinophils (*10^9 cells/L)†		0.3 (0.1-0.6)	0.1 (0.1-0.4)	0.4 (0.1-0.7)	0.013
Blood eosinophils (*10^9 cells/L)	<0.3 (%)	46.6	59.5	42.6	0.055
	≥0.3 (%)	53.4	40.5	57.4	
Bronchiectasis (%)		24.8	34.5	21.7	0.17
Nasal polyposis (%)		51.5	50	52	0.82
Chronic rhinosinusitis (%)		62.8	64.3	62.3	0.82

* Mean SD

† Median IQR

˜ Calculated for former smokers.

‡ Calculated for patients receiving OCS maintenance treatment on baseline, N=122.

Abbreviations: ACQ: Asthma Control Questionnaire, FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced Expiratory Volume in 1 second, ICS: Inhaled

Corticosteroids, IQR: interquartile range, OCS: Oral corticosteroids (prednisone equivalents)

Table 2: Clinical outcomes to benralizumab treatment for the total population, and stratified for non-responders and responders.

Variable	Total population (N=192)	Non-responders (N=48)	Responders (N=144)	P-value
Annual exacerbation frequency at baseline*	3 (2;5)	3 (2;4)	3 (2;5)	0.51
Annual exacerbation frequency after 1 year*	0 (0;1)	2 (1;2)	0 (0;0)	<0.001
Change in annual exacerbation frequency after 1 year*	-2 (-3;-1)	-1 (-2;0)	-2 (-4;-2)	<0.001
Maintenance OCS dose at baseline (mg/day)*	5 (0;10)	5 (0;17.5)	5 (0;10)	0.32
Maintenance OCS dose after 3 months (mg/day)*	0 (0;5)	5 (0;15)	0 (0;5)	0.001
Change in maintenance OCS dose after 3 months (mg/day)*	0 (-5;0)	0 (-5;0)	-2.5 (-5;0)	0.007
Maintenance OCS dose after 1 year (mg/day)*	0 (0;5)	5 (0;15)	0 (0;0)	<0.001
Change in maintenance OCS dose after 1 year (mg/day)*	-2. 5 (-6.25;0)	0 (-5;0)	-3.75 (-7.5;0)	0.002
ACQ-6-score baseline*	2.17 (1.67;3.17)	2.5 (1.85;3.33)	2.17 (1.5;3.1)	0.054
ACQ-6-score after 3 months*		2.5 (1.15;3.09)	1.0 (0.43;1.57)	<0.001
Change in ACQ-6-score after 3 months*	-0.83 (-1.57;-0.17)	-0.17 (-0.81;0.38)	-1 (-1.72;-0.34)	<0.001
ACQ-6-score after 1 year*	1 (0.5;1.83)	1.92 (1.09;2.6)	0.71 (0.33;1.57)	<0.001
Change in ACQ-6-score after 1 year*	-0.96 (-1.66;-0.17)	-0.17 (-1.18;0.34)	-1.04 (-1.67;-0.5)	<0.001
FEV$_1$ baseline (%predicted)*	72 (57;85)	70.3 (51;79)	72 (60;86)	0.088
FEV$_1$ after 1 year (%predicted)*	80 (66-96)	70.5 (49;82)	82 (66.1;99)	0.012
Change in FEV$_1$ after 1 year (%predicted)*	4 (-1.41;12.23)	1.5 (-1.5;6.5)	5.3 (-1;16.7)	0.085

Abbreviations: ACQ: Asthma Control Questionnaire, FEV$_1$: Forced Expiratory Volume in 1 second, OCS: Oral corticosteroids (prednisone equivalents), OR:

Odds ratio.

*: Median (IQR)

Table 3: Univariate logistic regression analysis predicting long-term benralizumab response.

Variables at baseline	OR (95%CI)	P-value
Male gender	1.81 (0.93-3.54)	0.082
Body mass index (kg/m²)	0.97 (0.91-1.03)	0.26
Age (years)	1.00 (0.98-1.03)	0.99
Former smoker	0.71 (0.37-1.38)	0.32
Non-atopic asthma	1.05 (0.52-2.11)	0.90
Adult onset asthma	0.63 (0.29-1.38)	0.25
Exacerbation frequency year before start (exacerbations per year)	1.05 (0.93-1.19)	0.43
ICS dose (mg, fluticasone equivalents)	1.00 (0.99-1.00)	0.27
OCS dose (mg/day)*	0.97 (0.94-1.01)	0.076
No previous biologic	3.87 (1.83-8.17)	<0.001
ACQ-6 score	0.74 (0.53-1.02)	0.063
FEV$_1$ prebronchodilator (%predicted)	1.01 (1.00-1.03)	0.13
Blood eosinophils (*10^9 cells/L)	1.47 (0.76-2.84)	0.26
Blood eosinophils ≥0.300 *10^9 cells/L	1.98 (0.98-4.00)	0.058
Nasal polyposis	0.92 (0.45-1.88)	0.83
Chronic rhinosinusitis	1.09 (0.53-2.25)	082
Variables at 3 months	**OR (95%CI)**	**P-value**
OCS dose (mg/day)*	0.89 (0.84-0.94)	<0.001
ACQ-6 score	0.34 (0.24-0.50)	<0.001

*: Patients without maintenance OCS have an OCS dose of 0 mg/day. Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, FEV$_1$:

Forced Expiratory Volume in 1 second, ICS: Inhaled Corticosteroids, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio.

Table 4: Multivariable logistic regression analysis, including baseline and 3 months characteristics (right), predicting long-term benralizumab response, as compared to a model including baseline characteristics only (left).

Variable	Baseline only		Baseline and 3 months	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Male gender	1.54 (0.71-3.32)	0.28	1.80 (0.69-4.72)	0.23
OCS dose at baseline (mg/day)	0.98 (0.94-1.02)	0.27	1.00 (0.94-1.06)	0.94
No previous biologic	3.61 (1.47-8.85)	0.005	2.84 (1.00-8.06)	0.051
ACQ-6 score at baseline	0.84 (0.56-1.25)	0.38	1.58 (0.88-2.81)	0.13
Baseline blood eosinophils ≥0.300 *10^9cells/L	1.22 (0.54-2.79)	0.64	1.25 (0.47-3.32)	0.66
FEV_1 prebronchodilator (%predicted)	1.01 (0.99-1.02)	0.61	1.01 (0.98-1.03)	0.65
OCS dose at 3 months (mg/day)*	-	-	0.91 (0.83-0.99)	0.031
ACQ-6 score at 3 months	-	-	0.32 (0.19-0.54)	<0.001
Area under ROC (95%CI)	**0.72 (0.63-0.80)**	**<0.001**	**0.85 (0.78-0.92)**	**<0.001**

*: Patients without maintenance OCS have an OCS dose of 0 mg/day. Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, FEV_1:

Forced Expiratory Volume in 1 second, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio, ROC: Receiver-Operating Characteristic.

Table 5: Development of a prediction tool, predicting long-term benralizumab response.

Variable		Rounded points	OR (95%CI)	P-value
Female gender		0	Ref.	
Male gender		2	1.57 (0.66-3.76)	0.31
Previous biologic		0	Ref.	
No previous biologic		3	2.74 (1.01-7.46)	0.048
Baseline blood eosinophils <0.300 *10^{9}cells/L		0	Ref.	
Baseline blood eosinophils ≥0.300 *10^{9}cells/L		1	1.02 (0.40-2.61)	0.97
FEV$_1$ pred <80%		0	Ref.	
FEV$_1$ pred ≥80%		2	1.78 (0.70-4.53)	0.23
OCS dose at 3 months >7.5 mg/day*		0	Ref.	
OCS dose at 3 months ≤7.5 mg/day*		3	3.07 (1.15-8.19)	0.025
ACQ-6 score at 3 months	≤0.75	8	7.81 (2.38-25.61)	<0.001
	0.76-1.5	3	3.19 (1.14-8.94)	0.027
	>1.5	0	Ref.	
Area under ROC curve (95%CI)		-	**0.82 (0.75-0.89)**	<0.001

*: Patients without maintenance OCS have an OCS dose of 0 mg/day. Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, FEV$_1$:

Forced Expiratory Volume in 1 second, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio, ROC: Receiver-Operating Characteristic.

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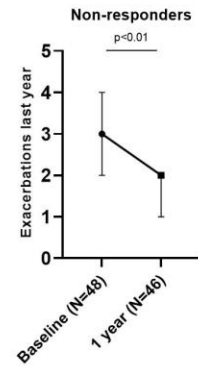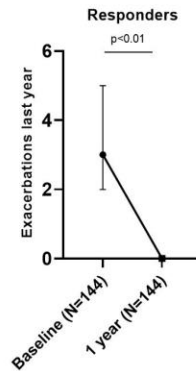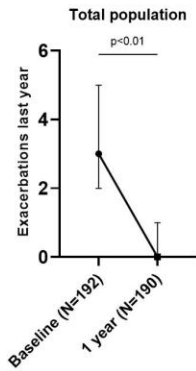
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Figure 1: Flow chart of selected patients.

Figure 2: Benralizumab effectiveness after 12 month. Legend to Figure 2: The figure describes the effect of benralizumab after 12 months on exacerbation rate, maintenance OCS-dose, ACQ-6-score, and pre-bronchodilator FEV1 (%predicted) for the total population (N=192), responders (N=144) and non-responders (N=48). The available number of patients per time point is shown on the X-axes in brackets.

Figure 3: Benralizumab response score Legend to Figure 3: The prediction tool combines baseline characteristics and outcomes at 3 months to predict long-term benralizumab response. Based on the score, the individual patient has a high (97% (95%CI 91-99)), intermediate (67% (95%CI 57-77)) or low (25% (95%CI 3-65)) probability of benralizumab response after 12 months. *Patients without maintenance OCS have an OCS-dose of 0 mg/day.
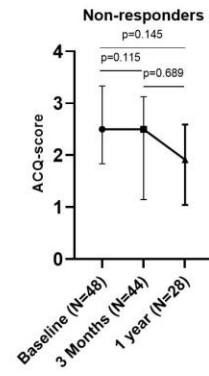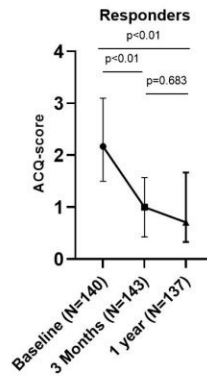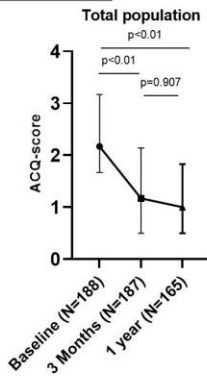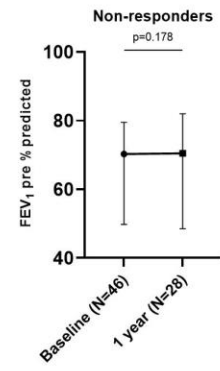
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┌─────────────────────────┐
│ Patients included in RAPSODI │
│ registry 1 October 2020 N=814 │
└─────────────────────────┘
            │
            │──────────────────────→  ┌──────────────────────────┐
            │                          │ Patients without benralizumab │
            │                          │ N=594 │
            ▼                          └──────────────────────────┘
┌─────────────────────────┐
│ Patients who initiated benralizumab │
│ between 1 Apr 2018 and 1 Oct 2020 │
│ N=220 │
└─────────────────────────┘
            │
            │──────────────────────→  ┌──────────────────────────────┐
            │                          │ Patients without exacerbations and │
            │                          │ OCS at baseline N=28 │
            ▼                          └──────────────────────────────┘
┌─────────────────────────┐
│ Patients in data-analysis N=192 │
└─────────────────────────┘
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Exacerbation frequency

Total population / Responders / Non-responders panels showing Exacerbations last year, p<0.01 for all three.

OCS maintenance dose

Total population (p<0.01), Responders (p<0.01), Non-responders (p=0.302, p=0.545, p=0.252) panels showing OCS maintenance dose (mg/day).

ACQ-6 Score

Total population (p<0.01, p<0.01, p=0.907), Responders (p<0.01, p<0.01, p=0.683), Non-responders (p=0.145, p=0.115, p=0.689) panels showing ACQ-score.

FEV₁ pre-bronchodilator (%predicted)

Total population (p<0.01), Responders (p<0.01), Non-responders (p=0.178) panels showing FEV₁ pre % predicted.

Baseline visit	3 months visit	Probability of benralizumab response after 12 months
Gender: Male +2 Female +0 **Biologic history:** Benralizumab first biologic +3 Benralizumab NOT first biologic +0 **Baseline blood eosinophils:** ≥0.300 cells/L +1 <0.300 cells/L +0 **FEV$_1$ (%predicted):** ≥80% +2 <80% +0	**Maintenance OCS dose*:** ≤7.5 mg/day +3 >7.5 mg/day +0 **ACQ-score:** ≤0.75 +8 0.76-1.5 +3 >1.5 +0	**High** Score 12-19 **Intermediate** Score 3-11 **Low** Score 0-2

Supplementary file 1: Acknowledgements.

Supplementary file 2: Calibration plots.

Supplementary Figure 1: Calibration plots for the logistic regression model with baseline characteristics and baseline characteristics combined with 3 months.

Supplementary Table S1 : Performance of the prediction tool in the population.

Prediction score	Number of patients (N=170)*		
	Non-responders (N=37)	Responders (N=133)	
0	4	1	
1	0	0	
2	2	1	
3	7	8	
4	1	2	
5	5	6	
6	4	7	
7	3	7	
8	1	7	
9	5	7	
10	1	10	
11	2	6	
12	1	13	
13	0	11	
14	0	8	
15	1	14	
16	0	5	
17	0	7	
18	0	0	
19	0	13	
Prediction category	Prediction score	Non-responders (N=37)	Responders (N=133)	Likelihood ratio (LR)
Low	0-2	6 (75%, 95%CI 35-97)	2 (25%, 95%CI 3-65)	0.09
Intermediate	3-11	29 (32.6%, 95%CI 23-43)	60 (67.4%, 95% CI 57-77)	0.58
High	12-19	2 (2.7%, 95%CI 0.3-10)	71 (97.2%, 95%CI 91-99)	9.88

* N=170; complete cases in the data set.

Abbreviations: CI: Confidence Interval; LR: Likelihood Ratio, defined as the probability of this prediction category occurring, given being responder, divided by the probability of this prediction category occurring, given being non-responder.

Supplementary Table S2: Multivariable logistic regression analysis, 3 months characteristics (left), predicting long-term benralizumab response, as compared to a model including only the ACQ-6 at 3 months (right).

Variable	3 months only		ACQ at 3 months only	
	OR (95%CI)	P-value	OR (95%CI)	P-value
OCS dose at 3 months (mg/day)	0.92 (0.87-0.97)	0.008	-	-
ACQ-6 score at 3 months	0.39 (0.26-0.59)	<0.001	0.34 (0.26-0.50)	<0.001
Area under ROC (95%CI)	0.80 (0.72-0.88)		0.79 (0.71-0.86)	

Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio, ROC: Receiver-Operating Characteristic.