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Blood eosinophil count and FeNO to predict benralizumab effectiveness in real-life severe asthma patients

Hirofumi Watanabe, MD^a, Toshihiro Shirai, MD, PhD^a, Keita Hirai, PhD^{b,c}, Taisuke Akamatsu, MD, PhD^a, Hiromasa Nakayasu, MD^a, Kanami Tamura, MD^a, Toshihiro Masuda, MD^a, Shingo Takahashi, MD^a, Yuko Tanaka, MD^a, Yutaro Kishimoto, MD^a, Kyohei Oishi, MD^a, Mika Saigusa, MD^a, Akito Yamamoto, MD^a, Satoru Morita, MD^a and Kazuhiro Asada, MD, PhD^a

^aDepartment of Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan; ^bDepartment of Clinical Pharmacology and Genetics, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan; ^cLaboratory of Clinical Pharmacogenomics, Shizuoka General Hospital, Shizuoka, Japan

ABSTRACT

Objective: Benralizumab is a promising drug for severe uncontrolled asthma. This study aimed to clarify the effectiveness of benralizumab in a real-life setting.

Methods: Subjects included 24 patients with severe type 2 asthma who received benralizumab between April 2018 and July 2019. Changes in parameters, exacerbation frequency, and oral corticosteroid (OCS) use after 4 and 24 weeks of administration were examined. The parameters included the Global Evaluation of Treatment Effectiveness (GETE) scale, Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT), blood eosinophils, fractional exhaled nitric oxide (FeNO), and spirometry. The response to treatment was defined as follows: for patients with exacerbations or OCS use before treatment initiation, a reduction of $\geq 50\%$ in exacerbation frequency or OCS use; and for patients without exacerbations or OCS use, an improvement of ≥ 0.5 in ACQ scores and ≥ 3 in ACT scores, or of $\geq 10.38\%$ in FEV1.

Results: Twenty-one patients completed the treatment for 24 weeks. Excellent and good GETE scales and ACQ and ACT improvement were found in 67% of the patients at 4 weeks, and the effect continued until 24 weeks. The patients' rate with exacerbations was significantly reduced compared to the previous 24 weeks before administration. In 17 patients receiving OCS, the use could be reduced or quit in 14 patients. Overall, 16 patients (76.2%) met the responder definition and could be predicted by the baseline eosinophil count and FeNO levels with the best cutoff values of 100/ μL and 40 ppb, respectively.

Conclusions: Blood eosinophil and FeNO could predict benralizumab effectiveness.

Abbreviations: ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; ATS: American Thoracic Society; AUC: area under the curve; ERS: European Respiratory Society; FeNO: fractional exhaled nitric oxide; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GETE: Global Evaluation of Treatment Effectiveness; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; LABA: long-acting β_2 -agonists; MCID: minimal clinically important difference; OCS: oral corticosteroid; ROC: receiver operating characteristics

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Introduction

A Dutch population survey of people ≥ 18 years with asthma found that 24% of the total patients received Global Initiative for Asthma (GINA) Steps 4 and 5 treatment, 17% had the Steps 4 and 5 treatment with poor symptom control as difficult-to-treat asthma, and 3.7% had the Steps 4 and 5 treatment with poor symptom control, and good adherence and inhaler technique as severe asthma (1). A Japanese health insurance database study found that

823 of the total 10 579 patients (7.8%) with ongoing treatment had severe asthma and 267 patients (2.5%) had severe uncontrolled asthma (2); the prevalence of severe asthma seems comparable between Europe and East Asia. Severe uncontrolled asthma patients required hospitalization (13.7%), were prescribed oral corticosteroid (OCS) (67.4%), and the yearly total medical expenses were great (8,346 USD) (2). Characteristic asthma features in Japan include public health insurance for the whole nation, a

geographically narrow country, and thus accessibility to hospitals and specialists, leading to the low asthma mortality of 1.2 per 100 000 people (3). Low prevalence of obesity (body mass index ≥ 30 kg/m²) of 5% to 7% and high prevalence of type 2 asthma (>80%) are also characteristic features.

Benralizumab, an anti-IL-5 receptor α antibody, has been available since 2018 in Japan and is widely used for severe asthma treatment. The European Respiratory Society (ERS)/American Thoracic Society (ATS) severe asthma guidelines suggest using benralizumab for severe uncontrolled adult eosinophilic asthma phenotypes and using a blood eosinophil cut-point $\geq 150/\mu\text{L}$ to guide anti-IL-5 initiation in adult patients with severe asthma (4). The great benefits of benralizumab are more than a 50% reduction in exacerbations and maintenance oral corticosteroid (OCS) dose, whereas the effects on asthma control, quality of life, and forced expiratory volume in 1 s (FEV1) are modest. These recommendations are based on the previous randomized controlled trials, including SIROCCO (5), CALIMA (6), and ZONDA (7) studies. However, many severe asthma patients do not always meet the inclusion or exclusion criteria of clinical trials in clinical practice (8), suggesting the need to investigate the efficacy of biologics in a real-life setting. As potential predictors of good asthma response, GINA recommends higher blood eosinophils, a higher number of severe exacerbations in the previous year, adult-onset asthma, nasal polyposis, and maintenance OCS use at baseline (9). However, the best biomarker and blood eosinophil threshold that would predict response to anti-IL-5 pathway therapy is uncertain (4).

This study aimed to assess the effect of benralizumab on asthma control, pulmonary function, exacerbation frequency, and OCS use in severe asthma patients and clarify which biomarker could predict the effectiveness.

Materials and methods

Study design

This was a real-life, prospective, single-arm, open-label, observational study. Subjects included severe uncontrolled asthma patients who satisfied the ERS/ATS severe asthma guidelines (4) and were administered benralizumab at Shizuoka General Hospital between April 2018 and July 2019. Adherence to ongoing asthma treatment, including inhaled corticosteroid (ICS)/long-acting β_2 -agonists (LABA) and other

controller medications, was confirmed. The patients satisfied at least one of the following type 2 inflammation findings: blood eosinophils $\geq 150/\mu\text{L}$, fractional exhaled nitric oxide (FeNO) ≥ 20 ppb, sputum eosinophils $\geq 2\%$, clinically allergen-driven asthma, and need for maintenance OCS (9). All subjects were administered benralizumab (30 mg) at weeks 0 (baseline), 4, 8, 16, and 24.

Changes in parameters, including Global Evaluation of Treatment Effectiveness (GETE) scale (10), Asthma Control Questionnaire (ACQ) (11), Asthma Control Test (ACT) (12), blood eosinophil counts, FeNO, and spirometry, were examined after 4 and 24 weeks of administration. GETE scale is a physician's subjective assessment tool of clinical response. 'Excellent' and 'good' responses of the GETE scale were considered an improvement. The minimal clinically important differences (MCID) of ACQ and ACT were 0.5 and 3 points, respectively. FeNO was measured by using NIOX VERO (Aerocrine AB, Solna, Sweden). Spirometry was performed by using CHESTAC-33 (Chest M.I. Co. Ltd., Tokyo, Japan). According to the ERS/ATS severe asthma guidelines (4), the MCID of FEV1 from the baseline was set at 10.38% (13).

Exacerbations were defined as a worsening in asthma control requiring more than 3 days of OCS add-on treatment. Exacerbation frequency was assessed during 24 weeks before and after benralizumab treatment initiation. For patients with daily OCS use at baseline, the dose was assessed at 4 and 24 weeks. For patients with as-needed OCS use 24 weeks before treatment, the number of uses was assessed during 24 weeks after treatment initiation.

The responder to benralizumab treatment was defined as follows: for patients with past exacerbations or OCS use before benralizumab initiation, a reduction of $\geq 50\%$ in exacerbation frequency or OCS use; and for patients without past exacerbations or OCS use, an improvement of ≥ 0.5 in ACQ scores and ≥ 3 in ACT scores, or of $\geq 10.38\%$ in FEV1.

The study protocols were approved by the Institutional Review Board of Shizuoka General Hospital (date of approval: March 2, 2018; and No: SGHIRB#2017079), and written informed consent was obtained from the subjects before the study. A part of this study was published elsewhere (14).

Statistical analysis

The quantitative data were summarized as median with range. The Wilcoxon signed-rank test was used

to compare changes between baseline and 4 or 24 weeks. Spearman's rank correlation coefficients were used to assess the correlations between variables. The Fisher's exact test was used to compare the categorical variables between groups. Receiver operating characteristics (ROC) analysis was used to determine optimal cutoff values of baseline blood eosinophil count for predicting 10.38% FEV1 improvement at 4 and 24 weeks and baseline values for predicting benralizumab responders. All analyses were performed with EZR software (version 1.27, Saitama Medical Center, Jichi Medical University, Saitama, Japan) (15). A two-tailed p values of < 0.05 was considered statistically significant.

Results

There were 14 patients with severe eosinophilic asthma, of the total 24 patients with severe type 2 asthma. The demographic data are shown in Table 1. The median body mass index was 23.1 kg/m². Half of the patients were atopic, showing at least one positive response to common inhalant allergens. Five patients had eosinophilic sinusitis. Mepolizumab was given previously in 5 patients, but more than 6 months had passed until benralizumab treatment initiation. Of the 24 patients

who completed the treatment for 4 weeks, 3 patients opted out of the treatment due to economic reasons.

The improvement of the GETE scale (excellent and good), ACQ, and ACT scores were found in 67% of the patients, respectively, at 4 weeks, and the effect continued until 24 weeks (Figure 1). The median ACQ and ACT scores improved significantly at 4 and 24 weeks than baseline values (Figure 1 and Table 2).

There was a moderate correlation between baseline blood eosinophil count and FeNO levels ($\rho = 0.420$). Baseline FeNO levels were significantly higher in patients with eosinophil count $\geq 150/\mu\text{L}$ than those with eosinophil count $< 150/\mu\text{L}$ (median: 42.0 ppb versus 21.5 ppb, $p = 0.024$). Blood eosinophil counts significantly reduced to $0/\mu\text{L}$ at 4 weeks, whereas FeNO levels did not change. FVC and FEV1 tended to improve, but they did not reach statistical significance (Figure 2 and Table 2). There was a positive correlation between the baseline blood eosinophil count and the improvement rate of FEV1 at 4 weeks ($\rho = 0.684$) and 24 weeks ($\rho = 0.730$), respectively. There were 9 patients with FEV1 improvement $\geq 10.38\%$ at 4 weeks, and the baseline eosinophil count was significantly higher in these patients than in the remaining 15 patients: median values: $569/\mu\text{L}$ versus $133/\mu\text{L}$, respectively. However, there was no difference in the demographic data, asthma control, IgE, or FeNO levels. ROC analysis revealed that the baseline eosinophil count predicted the patients with FEV1 improvement with the best cutoff value of $205/\mu\text{L}$ at 4 weeks and $261/\mu\text{L}$ at 24 weeks, respectively.

In 21 patients who completed benralizumab treatment for 24 weeks, the number of patients with exacerbations was significantly reduced compared to that 24 weeks before treatment (52.3% versus 14.3%, $p = 0.02$) (Table 2 and Figure 3). In addition, in the 17 patients with daily or as-needed OCS use, the use was reduced or quit in 14 (82.4%) patients (Table 2 and Figure 4).

The overall response rate at 24 weeks was 16 (6 males and 10 females) of 21 patients (76.2%) (Figure 5). Baseline blood eosinophil count was significantly higher in responders than in non-responders: median, $261/\mu\text{L}$ and $22/\mu\text{L}$, respectively. In addition, there were 5 responders with baseline eosinophil count $< 150/\mu\text{L}$. However, there was no difference in the demographic data, asthma control, IgE, FeNO levels, or pulmonary function. ROC analysis revealed that baseline eosinophil count and FeNO levels could predict the response to benralizumab at 24 weeks with the best cutoff values of $100/\mu\text{L}$ and 40 ppb, respectively. (Figure 6).

Table 1. Patient characteristics at baseline.

	N = 24	
Age, years	55	(28, 82)
Sex, male	9	(38)
Body mass index (kg/m ²)	23.1	(16.5, 30.3)
Duration of disease (years)	26	(2, 70)
Smoking history		
Never smoker	17	(71)
Ex-smoker	7	(29)
Current smoker	0	(0)
Atopy	12	(50)
Allergic rhinitis	8	(33)
Sinusitis	9	(38)
Eosinophilic sinusitis	5	(21)
Asthma Control Questionnaire	2.4	(0.4, 5.4)
Asthma Control Test	15	(7, 24)
Blood eosinophil (/μL)	228	(0, 5191)
Total IgE (IU/mL)	69	(5, 678)
FeNO (ppb)	29.5	(5.0, 152.0)
FVC (L)	2.35	(1.29, 4.21)
FVC, % predicted	89.8	(8.6, 112.1)
FEV1 (L)	1.53	(0.62, 2.65)
FEV1, % predicted	72.2	(32.6, 111.0)
Medication		
ICS/LABA	24	(100)
LTRA	20	(83)
Tiotropium	16	(67)
OCS	17	(71)
Daily use	9	(38)
As needed use	8	(33)
Biologics past use: mepolizumab	5	(24)

Median (range) or frequency (percentage). Abbreviations: FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroid.

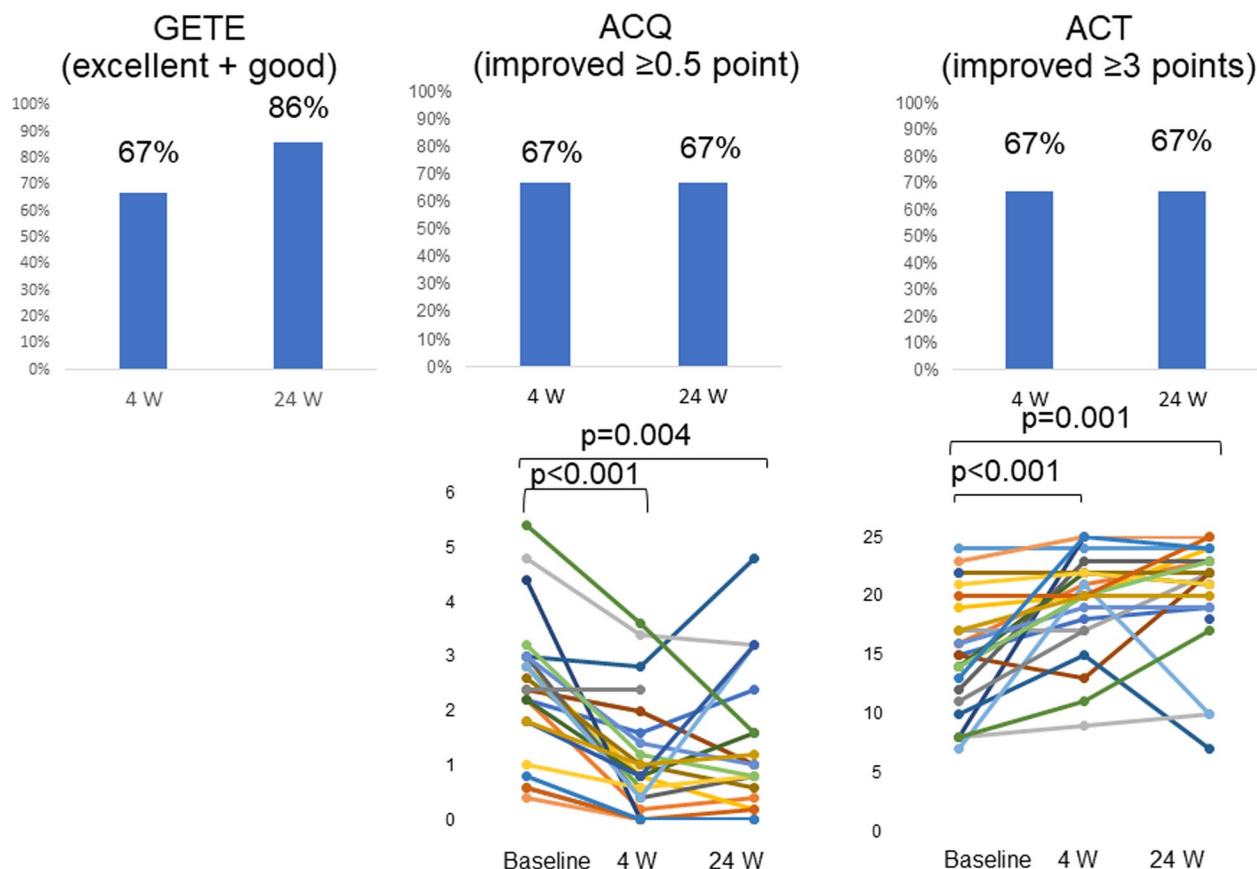


Figure 1. Improvement rate of GETE, ACQ, and ACT at 4 and 24 weeks (upper panel) and changes from baseline to 4 and 24 weeks after treatment with benralizumab (lower panel). ACQ and ACT improved significantly after treatment initiation and continued to 24 weeks. Abbreviations: ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; GETE, global evaluation of treatment effectiveness.

Table 2. Changes in parameters, exacerbation frequency, and OCS use after benralizumab treatment initiation.

	Baseline	4 weeks	24 weeks
Asthma Control Questionnaire	2.4 (0.4, 5.4)	0.8 (0, 3.6)*	0.9 (0, 4.8)*
Asthma Control Test	15 (7, 24)	20 (9, 25)*	22 (7, 25)*
Blood eosinophil (/μL)	228.5 (0, 5191)	0 (0, 13)*	0 (0, 0)*
FeNO (ppb)	29.5 (5, 152)	40 (9, 160)	32 (9, 173)
FVC (L)	2.35 (1.29, 4.21)	2.64 (1.50, 4.06)	2.84 (1.52, 3.74)
FVC, % predicted	89.8 (8.6, 112.1)	95.0 (60.0, 118.8)	95.8 (58.5, 110.6)
FEV1 (L)	1.53 (0.62, 2.65)	1.74 (0.61, 2.57)	1.83 (0.80, 2.60)
FEV1, % predicted	72.2 (32.6, 111.0)	80.6 (26.8, 117.4)	82.7 (36.7, 105.8)
Exacerbation, yes/no	11/10	3/18*	5
Frequency, per patient	3.0	0.3	4
OCS use	17		5
Daily	9	4	4
Dose, mg/day**	4.8 ± 7.3	1.6 ± 3.7	1.5 ± 3.2*
As needed	8		1

Median (range) or frequency (percentage). Abbreviations: FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; OCS, oral corticosteroid. * $P < 0.05$ versus baseline or during 24 weeks before treatment. **mean $\pm$ SD

Discussion

This study found that asthma control, but not pulmonary function, improved significantly, and exacerbation frequency and OCS use were reduced after 24 weeks of benralizumab treatment in 21 severe type 2 asthma patients. The overall response rate was 76.2% and was predicted by the baseline eosinophil count and FeNO levels.

A recent real-world retrospective study of 130 severe eosinophilic asthma patients treated with benralizumab for 48 weeks found that asthma control, quality of life, and FEV1 improved significantly, and exacerbation frequency and OCS use were reduced (16). Response to treatment was defined as reducing $\geq 50\%$ in annualized exacerbation rate or OCS dose, showing a response rate of 86.2%. This study's response rate seemed

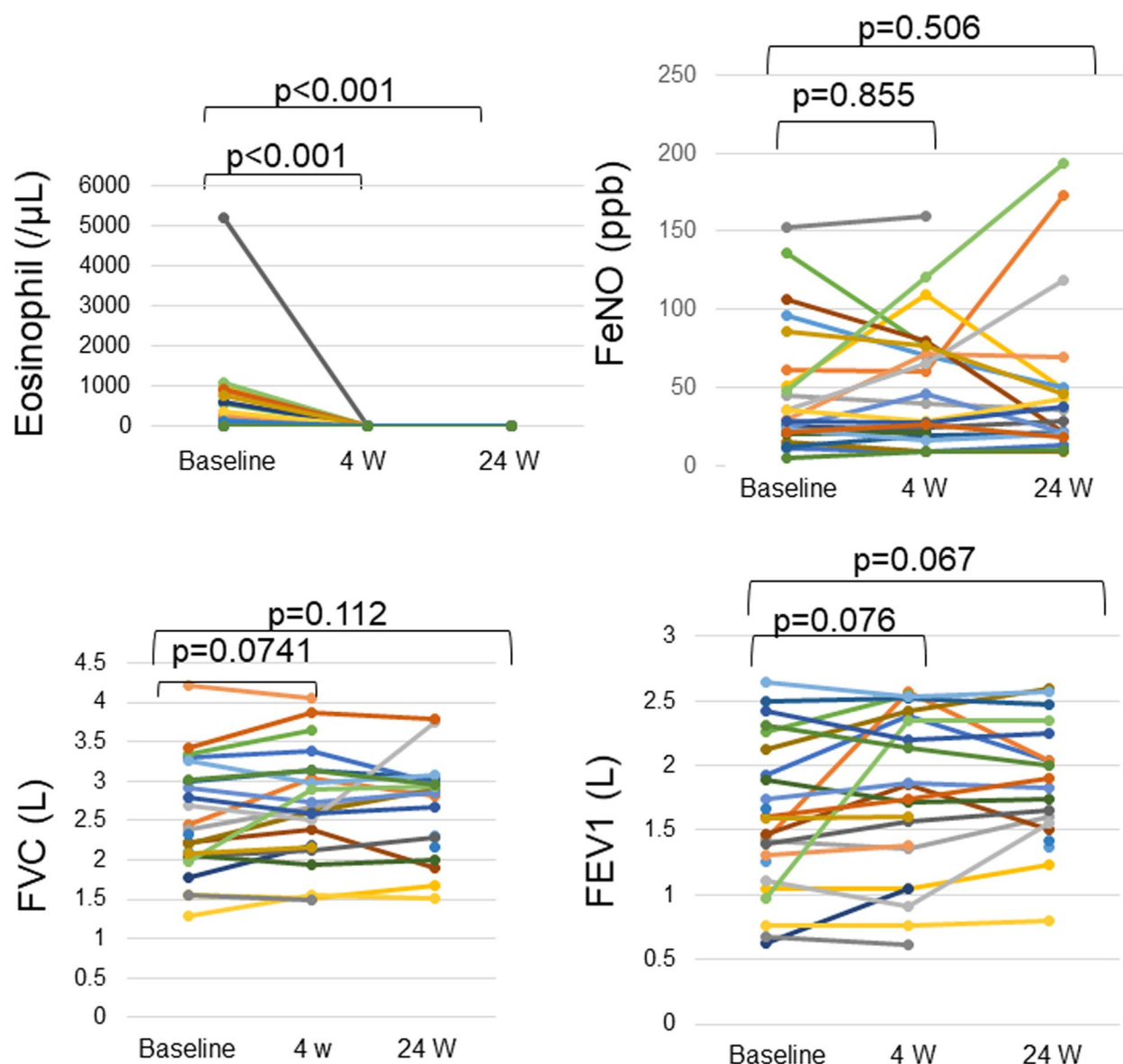


Figure 2. Changes in parameters from baseline to 4 and 24 weeks after treatment with benralizumab. Eosinophil count reduced significantly after treatment initiation. However, there were no significant changes in FeNO, FVC, or FEV1. Abbreviations: FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

comparable, although asthma phenotype and the responder's definition were different, and a simple comparison was not possible. Considering other previous studies (17–19), benralizumab is also effective in a real-life setting.

The ERS/ATS severe asthma guidelines recommend using a blood eosinophil cut-point $\geq 150/\mu\text{L}$ to guide anti-IL-5 initiation in severe eosinophilic asthma (4). This study found that baseline blood eosinophil count was significantly higher in responders than in non-responders: median, $261/\mu\text{L}$ and $22/\mu\text{L}$, respectively. However, ROC analysis revealed a lower eosinophil count of $100/\mu\text{L}$ as a threshold that would predict response to benralizumab. Possible

explanations for this may be the presence of 5 responders with baseline eosinophil count $< 150/\mu\text{L}$ and the difference between severe eosinophilic asthma and severe type 2 asthma as inclusion criteria in this study.

A recent real-world retrospective study analyzed the relationship between FeNO and the effectiveness of mepolizumab and benralizumab in 229 severe eosinophilic asthma patients and found that baseline FeNO did not predict response to the therapies, with equivalent treatment effectiveness in patients with very high and more modest FeNO levels (20). Contrary to the anti-IL-4/13 receptor α antibody, dupilumab, benralizumab does not reduce FeNO

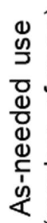


Figure 4. Change in OCS use after 24 weeks treatment with benralizumab (upper panel) and changes in the daily dose (lower left) and as-needed use of OCS (lower right). OCS use was reduced or quit in 14 of 17 (82.3%) patients. Abbreviation: OCS, oral corticosteroid.

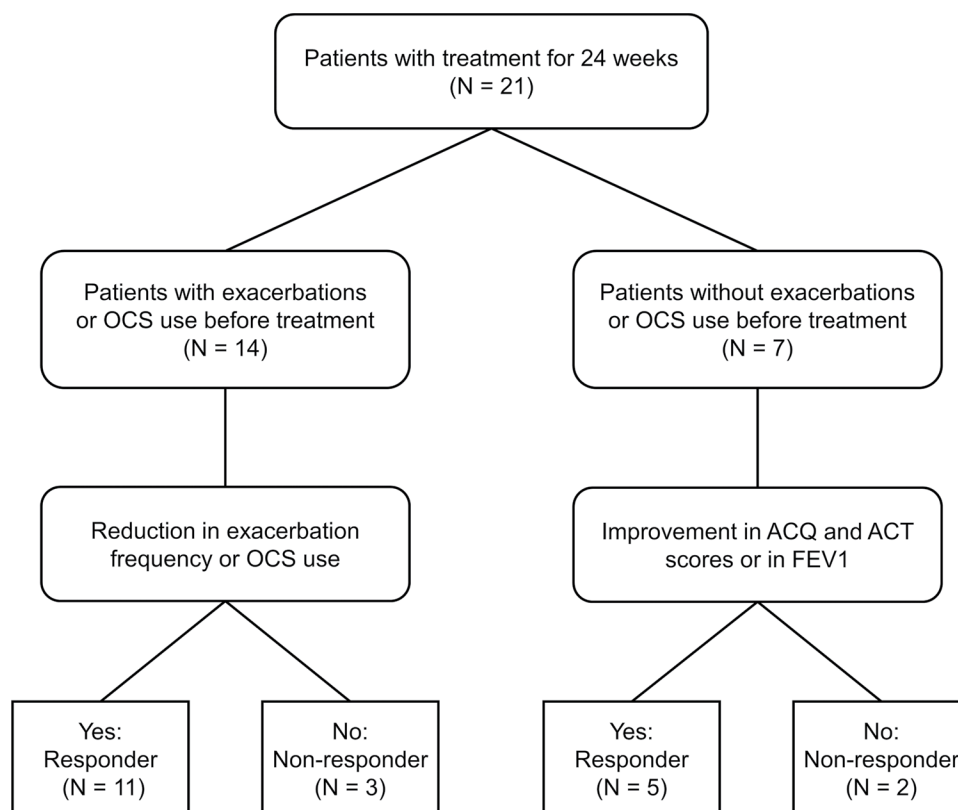


Figure 5. Patient flow to detect responders to benralizumab treatment at 24 weeks. Abbreviations: ACT, asthma control test; ACQ, asthma control questionnaire; FEV1, forced expiratory volume in 1 s; OCS, oral corticosteroid.

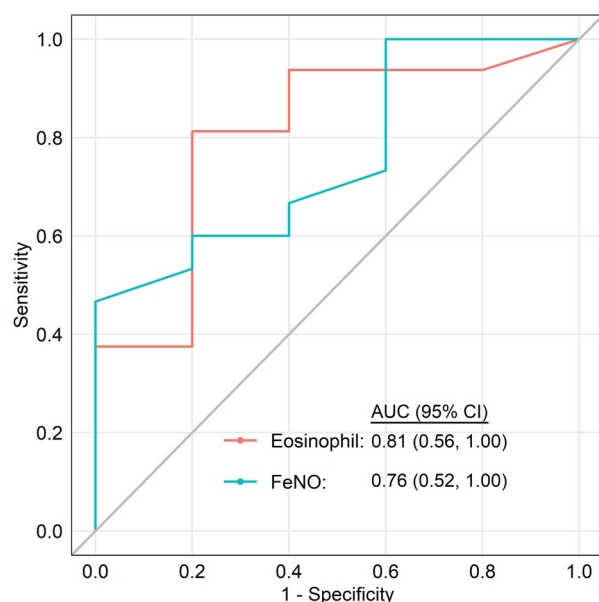


Figure 6. ROC analysis predicting overall response to benralizumab treatment at 24 weeks. Baseline eosinophil count and FeNO levels could predict the overall response with the best cutoff values of 100/ μ L and 40 ppb, respectively. Abbreviations: AUC, area under the curve; FeNO, fractional exhaled nitric oxide.

levels. In this regard, a high FeNO level is a characteristic of severe eosinophilic asthma (21) and reflects eosinophilic airway inflammation (22). We found a correlation between baseline blood eosinophil count and FeNO levels, and significantly higher FeNO levels in patients with blood eosinophil count $\geq 150/\mu\text{L}$. We speculate that FeNO can predict benralizumab effectiveness in severe type 2 asthma patients with high blood eosinophil counts and FeNO levels, as shown in this study. However, its effectiveness in patients with low FeNO levels suggests that FeNO may provide limited additional prognostic information for patients with severe eosinophilic asthma (23,24).

The ERS/ATS severe asthma guidelines concluded that the effects of benralizumab on asthma control, quality of life, and FEV1 were modest and did not meet the MCID threshold (4). This study found that ACQ and ACT scores improved more than MCID, whereas FEV1 did not reach statistical significance. However, the baseline eosinophil count could predict more than MCID ($\geq 10.34\%$) improvement in FEV1 at 4 and 24 weeks, suggesting the usefulness in an individual patient with severe type 2 asthma in a real-life setting.

Recently, we found that benralizumab restored gene expression in blood T cells, including HDAC2, NFE2L2, GLCC1, and PTEN, involved in steroid sensitivity in 17 patients of this study (25). These findings suggest that benralizumab might be effective in some patients with steroid resistance, and natural antioxidant therapy that can activate NFE2L2 might help manage severe asthma, although future work is needed.

The major limitation of this study is the small sample size. Other limitations include a single-center study, no control group, and uncertain generalizability of the findings. In addition, caution must be paid for the inclusion criteria of severe type 2, but not eosinophilic, asthma. Finally, as described above, the role of baseline FeNO levels as a predictor of treatment response is limited. However, we believe that these findings will aid in using benralizumab for the real-life treatment of severe type 2 asthma.

Conclusions

Benralizumab treatment for 24 weeks improved asthma control and reduced exacerbation frequency and OCS use in 21 severe type 2 asthma patients. Based on the effectiveness of reducing exacerbation and OCS use, or more than MCID improvement in asthma control and FEV1, the overall response rate to benralizumab was 76.2%. The baseline eosinophil count and FeNO levels could predict the responders.

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Each author's role: (1) conception and design of the study: T.S., T.A., K.H.

(2) data generation: H.W., T.S., T.A., H.N., K.T., T.M., S.T., Y.T., Y.K., K.O., M.S., A.Y., S.M., K.A., (3) analysis and interpretation of the data: H.W., T.S., T.A., K.H., (4) preparation of the manuscript: H.W., T.S., K.H.

Conflicts of interest

T.S. reports personal fees from AstraZeneca Japan, GlaxoSmithKline Japan, Boehringer Ingelheim Japan, and Novartis Pharma outside of the submitted work. The other authors have nothing to disclose.

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