

Effects of Benralizumab on Three-Dimensional Computed Tomography Analysis in Severe Eosinophilic Asthma

Fumito Tsubokawa^a Toshiyuki Koya^a Yui Murai^a Kentaro Tanaka^a
Yuchi Tsutsui^a Shun Naramoto^a Natsumi Sakai^a Ami Aoki^a Kenjiro Shima^a
Yosuke Kimura^a Satoshi Watanabe^a Takashi Hasegawa^b Toshiaki Kikuchi^a

^aDepartment of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; ^bDepartment of General Medicine, Niigata University Medical and Dental Hospital, Niigata, Japan

Keywords

Benralizumab · Severe asthma · Airway wall thickening · Total airway count · Blood eosinophil

Abstract

Introduction: Benralizumab, an anti-interleukin-5 receptor chain monoclonal antibody, is used to treat severe asthma and control asthma symptoms or exacerbations. The aim of this study was to examine the changes in airway morphology using computed tomography (CT) images in accordance with clinical efficacy following the administration of benralizumab. **Methods:** The clinical efficacy of benralizumab was evaluated in 11 patients with severe asthma by analyzing the changes in parameters, such as the asthma control test, asthma quality of life questionnaire, pulmonary function, and exacerbation count. We also investigated the airway wall thickness of the right bronchus (B1) and the total airway count (TAC) using CT images. **Results:** Most patients treated with benralizumab showed improvements in asthma symptoms and exacerbations. CT imaging analyses showed a decrease

in the right B¹ airway wall thickness and an increase in the TAC. Correlations between blood eosinophil count and changes in CT imaging were observed. **Discussion/Conclusion:** The data suggested that benralizumab has the potential to improve airway wall thickening and ventilation by alleviating the obstruction and clearing an obstructed airway.

© 2022 S. Karger AG, Basel

Introduction

Asthma is an inflammatory disease characterized by the narrowing and thickening of the walls of the airways [1]. Wall thickening has been evaluated as a sign of airway remodeling and is speculated to be caused by chronic airway inflammation. Moreover, the levels of forced expiratory volume in 1 s (FEV₁) and peak expiratory flow rate were used as indices of obstructive disorders. Although

Edited by: H.-U. Simon, Bern.

these indices assess airway obstruction, they cannot help examine airway wall thickening or the presence of mucus plugs. Computed tomography (CT) is an extremely useful tool for the three-dimensional evaluation of the airway. Thickening of airway walls and reduction of the airway lumen area have been noted using CT images, particularly in patients with severe asthma [2–4].

There are several reports on airway inflammation and airway wall thickenings, including analysis of the correlation between airway wall thickening and the fraction of exhaled nitric oxide (FeNO) [5], an important biomarker for type 2 airway inflammation [6]. Additionally, a direct correlation between peripheral blood or sputum eosinophils and the airway wall has been reported [7]. From both reports, it can be inferred that eosinophilic airway inflammation plays an important role in airway wall thickening. Moreover, Dunican et al. [8] reported a relationship between the sputum eosinophil ratio and the number of mucus plugs observed on a CT scan, suggesting that eosinophil peroxidase, an eosinophil granule protein, is associated with mucus plugs. Mucus plugs are speculated to cause airway obstruction and airflow limitation [9].

Benralizumab, a humanized monoclonal antibody for the interleukin-5 (IL-5) receptor α chain, is used to manage difficult-to-treat asthma in adults and is clinically effective in patients with high eosinophil counts. In phase 3 trials, an add-on treatment of benralizumab decreased asthma exacerbation, increased FEV₁, and nearly eliminated peripheral blood eosinophils [10, 11]. In addition, there have been some reports of the reduction of sputum and blood eosinophilia with benralizumab [12, 13]. However, there have been no reports of improvement in the morphological findings such as airway wall thickening and total airway counts (TACs) after the use of benralizumab.

In this study, we examined airway morphology using CT analysis in 11 cases before and after administering benralizumab. We reported that benralizumab reduced airway wall thickening and distinctly increased the total number of airways as determined by CT imaging.

Methods

Study Participants

The study involved 11 patients (6 women and 5 men) with a diagnosis of severe uncontrolled eosinophilic asthma, according to the ATS/ERS criteria [14], treated with benralizumab and underwent a CT before and 4–6 months after the start of benralizumab treatment at Niigata University Medical and Dental Hospital from

April 2018 to August 2020. Patients with a history of biological therapy before benralizumab treatment were excluded. This study was conducted in accordance with the ethical principles for medical research involving human subjects, the Declaration of Helsinki, and with the approval of the Ethics Committee of Niigata University (approval No. 2524). All participants provided written informed consent prior to enrollment.

Clinical Assessments

Before the initiation of benralizumab, all participants underwent a physical examination, Asthma Control Test (ACT; Japanese version), Asthma Quality of Life Questionnaire (AQLQ; Japanese version), pulmonary function test, measurement of the fraction of exhaled nitric oxide (FeNO) level, peripheral blood eosinophil count, and measurement of total immunoglobulin E (IgE) levels. After 4 months of treatment, the participants were examined using the same procedures to measure the efficacy of benralizumab. We also evaluated for asthma exacerbation, identified by the use of a systemic corticosteroid due to asthma symptoms for 12 months before and after the administration of benralizumab.

Pulmonary function tests were performed using a spirometer (SpiroSift SP-470; Fukuda Densi Co., Ltd., Tokyo, Japan) following the American Thoracic Society (ATS) guidelines. FeNO level was measured using a nitric oxide analyzer (NIOX VERO® Circassia AB, Uppsala, Sweden), in accordance with a previous mutual consensus statement from the ATS/European Respiratory Society [15].

Chest CT and Image Analysis

Multidetector-row CT (MDCT) imaging was performed mainly using an MDCT machine, SOMATOM Force (Siemens, Munich, Germany). All images were obtained in the supine position during full inspiration breath-holds. Images were reconstructed using a slice thickness at 1 mm slice intervals. Three-dimensional CT images of airway trees reconstructed from MDCT images were obtained using image-analyzing software (SYNAPSE VINCENT; Fujifilm Corporation, Tokyo, Japan). Reconstruction of the bronchial pathway was performed using the software as previously reported [5]. Airway measurements were noted in one bronchus (B¹) in the right lung according to methods reported previously [16] and the analysis was performed by two respiratory physicians who were blinded to the patient's data. For each case, four levels of the airways (third- [segmental], fourth- [subsegmental], fifth-, and sixth-generation bronchi) were identified by tracing the airway trees peripherally on the same trunk of each segmental bronchus. At the midpoint of each level of the airway, the wall area (WA) and airway inner luminal area (Ai) perpendicular to the long axis of the airway were automatically computed. WA was defined as the area between the outer and inner edges of the airway (Fig. 1a). WA was expressed as a percentage of a ratio (WA/outer area of the bronchus). To eliminate the potential influence of body size of each patient, Ai and WA were adjusted by BSA (Ai/BSA and WA/BSA, respectively), according to previous reports [2, 5, 17].

The total airway count was modified based on the previous report [18, 19]. Segmentation of the airway trees were skeletonized to obtain their centerlines using SYNAPSE VINCENT software. All the centerline branches between branching points were labeled and manually counted (Fig. 1b).

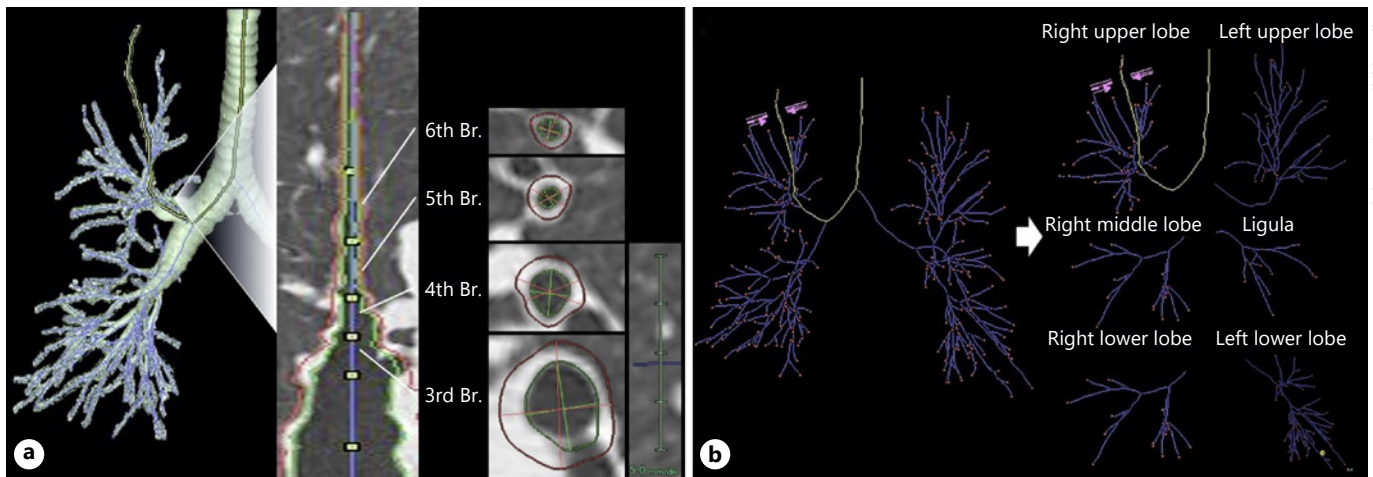


Fig. 1. Three-dimensional CT analysis of the airways. **a** Using three-dimensional airway tree images, longitudinal and short-axis images were reformatted. Red and green lines indicate the outer and inner edges of the airways, respectively. The areas within the green line and between the red and green lines are the airway inner luminal area and wall area, respectively. **b** The airway tree was automatically segmented from the original CT image. All branches of the centerline between branching points were labeled and counted manually. CT, computed tomography.

Statistical Analysis

The data are expressed as a median (minimum–maximum). Within-group (pre- and posttreatment) comparisons were conducted using Wilcoxon's signed rank test. The correlation between the morphological findings and clinical parameters was determined using Spearman's rank analysis. All statistical analyses were performed using JMP software, version 11 (SAS Institute, Inc., Tokyo, Japan). For all statistical analyses, the statistical significance was set at $p < 0.05$.

Results

The baseline data for all 11 patients are shown in Table 1. Five patients were men, the median age was 71 years, and the disease duration was 15 years. Six patients (55%) had chronic rhinosinusitis as comorbidity. The median ICS dose was 750 $\mu\text{g}/\text{day}$ (equivalent to fluticasone); however, none of the patients used maintenance oral corticosteroids. The median frequency of exacerbation in the previous year, defined as a systemic corticosteroid burst due to asthma symptoms, was five. The baseline median ACT and AQLQ scores were 18 and 4.75, respectively. The baseline blood eosinophil count was 780 per μL . The median IgE and FeNO levels were 533 U/L and 66.0 ppb, respectively. Most patients showed obstructive impairment based on the pulmonary function data.

WA and Ai from the third- to sixth-generation bronchi of the right bronchus B1 and TAC in the whole lung

Table 1. Summaries of clinical parameters of the subjects

Male	5 (45)
Age, years	71 (55–83)
Duration, years	15 (5–51)
BMI, kg/m^2	24.2 (18.5–32.0)
Smoking	
Never smoked	7 (64)
Past smoking	4 (36)
Atopic	7 (64)
CRS comorbidity	6 (55)
ICS, $\mu\text{g}/\text{day}$ (equivalent to fluticasone)	750 (400–1,000)
Maintenance OCS	0 (0)
Exacerbation, /year	5 (0–10)
ACT	18 (12–23)
AQLQ	4.75 (4.0–5.9)
Blood eosinophil, $/\mu\text{L}$	780 (530–2,559)
IgE, U/L	533 (6.4–16,000)
FeNO, ppb	66.0 (21–274)
%FEV ₁	71.0 (54.0–98.6)
FEV ₁ /FVC, %	66.3 (51.9–78.3)

Data are expressed as n (%) or median (minimum–maximum). BMI, body mass index; CRS, chronic rhinosinusitis; ICS, inhaled corticosteroid; OCS, oral corticosteroid; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; IgE, immunoglobulin E; FeNO, fraction of exhaled nitric oxide; FEV₁, percent forced expiratory volume in 1 s; FVC, forced vital capacity.

are shown in Table 2. We analyzed the correlation between the parameters of airway morphology in the third generation of B¹ and the clinical data, where none of them showed a significant correlation (Table 3). Furthermore,

Table 2. Three-dimensional CT analysis of airway morphology

	Third-generation bronchus	Fourth-generation bronchus	Fifth-generation bronchus	Sixth-generation bronchus
Ai, mm ²	17.6 (10.3–44.6)	9.6 (4.6–33.4)	3.7 (2.2–6.4)	2.7 (1.0–8.0)
Ai/BSA, mm ² /m ²	14.1 (6.7–28.8)	6.6 (3.7–18.0)	2.5 (1.3–5.2)	1.7 (0.6–5.8)
WA, mm ²	32.1 (19.1–54.0)	18.1 (11.3–48.6)	10.6 (4.0–16.2)	5.6 (2.8–16.7)
WA/BSA, mm ² /m ²	21.9 (11.9–31.1)	12.4 (7.4–26.4)	8.30 (2.4–11.7)	3.5 (2.3–12.0)
WA%, %	52 (43–77)	66 (57–77)	73 (60–78)	71 (63–88)
Right whole lung				
TAC	60 (21–132)			

Data are expressed as median (range). Ai, airway inner luminal area; WA, wall area; BSA, body surface area; TAC, total airway count.

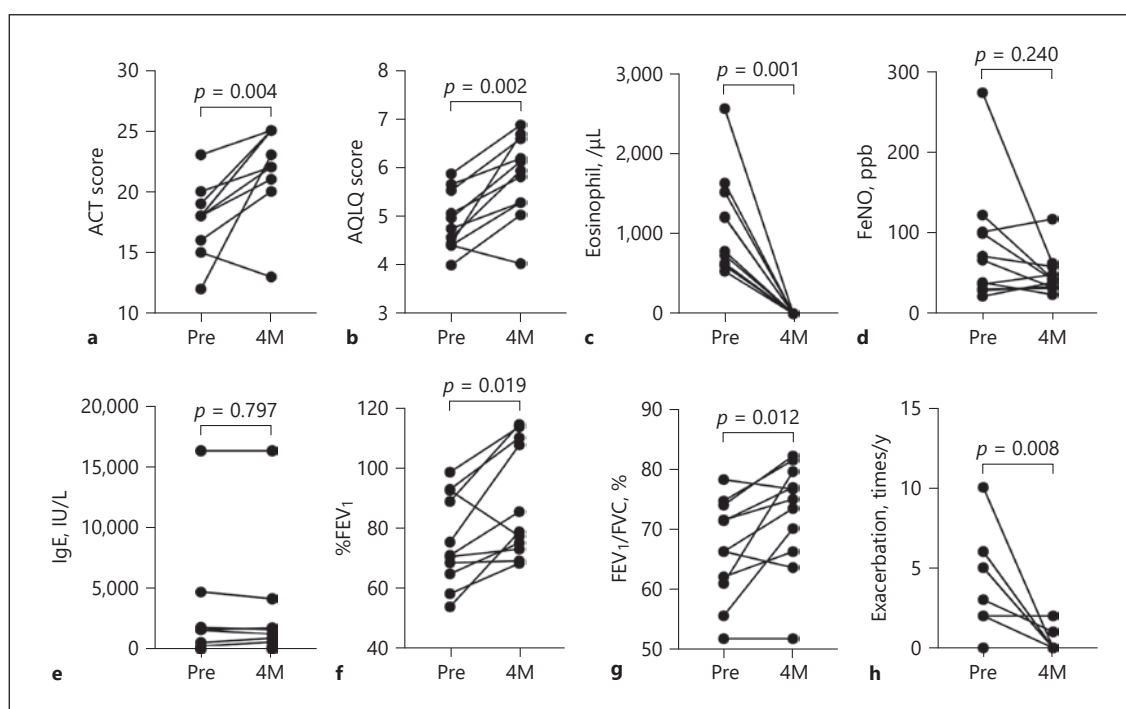


Fig. 2. Changes in clinical parameters and biomarkers with benralizumab treatment. Values were obtained before (“Pre”) and 4 months after (“4M”) benralizumab treatment. **a** ACT scores. **b** AQLQ scores. **c** Eosinophil count in peripheral blood. **d** FeNO. **e** IgE. **f** Percent forced expiratory volume in 1 s (%FEV₁). **g** FEV₁/FVC. **h** Frequency of asthma exacerbation in the previous year. The *p* values were calculated via Wilcoxon matched-pairs signed rank tests. ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; FeNO, fraction of exhaled nitric oxide; ppb, parts per billion. FVC, forced vital capacity.

none of the other generational parameters showed a significant correlation (data not shown).

We compared asthma symptoms, biomarkers, pulmonary function, and frequency of exacerbation in preadministration and 4 months after (4M-) administration of benralizumab (Fig. 1). The ACT and AQLQ scores sig-

nificantly increased compared to the pre-benralizumab group (Fig. 2a, b). Blood eosinophils in 4M-benralizumab dramatically decreased and reached zero, whereas the levels of total IgE and FeNO did not differ between the groups (Fig. 2c–e). The %FEV₁ and FEV₁/FVC increased significantly, while the frequency of exacerbation de-

Table 3. Correlation between airway morphology and clinical parameters

Parameter	Ai/BSA (3rd)	WA/BSA (3rd)	WA% (3rd)	TAC
Duration	0.32 (0.34)	−0.08 (0.82)	0.48 (0.09)	−0.21 (0.53)
%FEV ₁	−0.11 (0.75)	0.17 (0.62)	0.37 (0.26)	−0.15 (0.67)
%MMEF	−0.03 (0.95)	−0.05 (0.90)	0.19 (0.58)	−0.15 (0.67)
ACT	0.31 (0.36)	0.24 (0.48)	0.01 (0.98)	0.15 (0.66)
FeNO	−0.41 (0.21)	−0.09 (0.80)	0.18 (0.60)	−0.08 (0.82)
Blood eosinophil	−0.50 (0.12)	0.29 (0.39)	0.42 (0.19)	−0.57 (0.07)
Exacerbation	−0.11 (0.75)	0.15 (0.66)	−0.14 (0.67)	−0.12 (0.72)

Data are expressed as r (p value). Ai, airway inner luminal area; WA, wall area; BSA, body surface area; TAC, total airway count; %FEV₁, percent forced expiratory volume in 1 s; %MMEF, percent maximum mid-expiratory flow; ACT, Asthma Control Test; FeNO, fraction of exhaled nitric oxide.

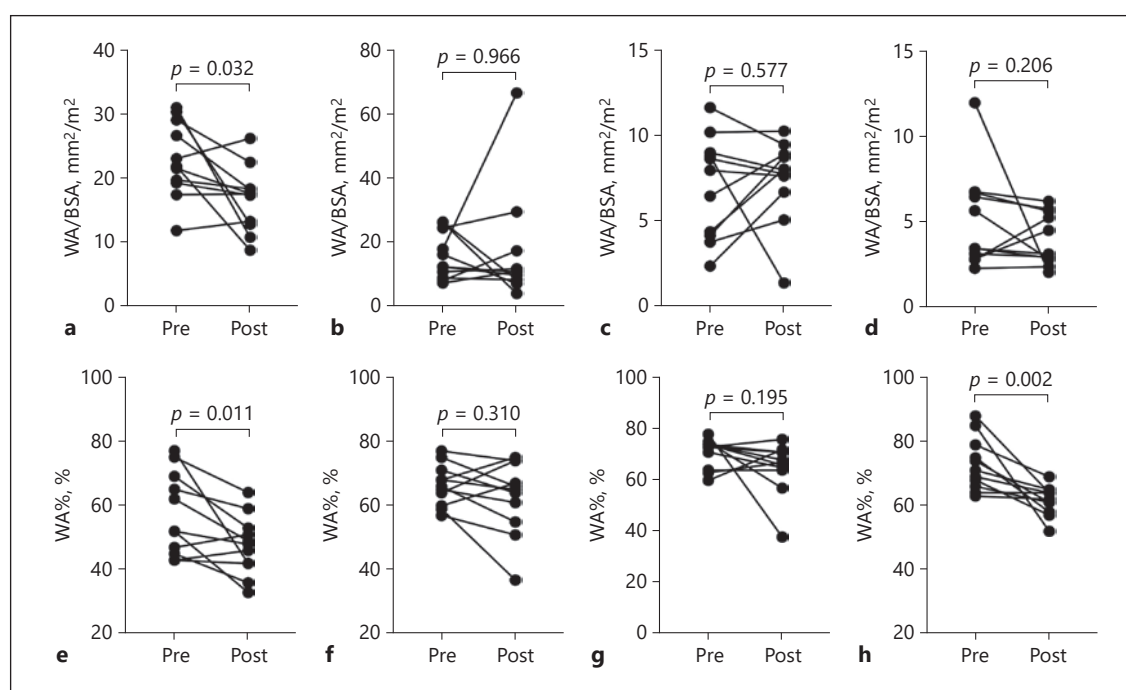


Fig. 3. Changes in the morphological parameters in CT with benralizumab treatment. Values were obtained before (“Pre”) and after (“Post”) benralizumab treatment. **a–d** WA/BSA. **e–h** WA%. **a, e** 3rd generation branch of right B1. **b, f** 4th generation. **c, g** 5th generation. **d, h** 6th generation. The p values were calculated via Wilcoxon matched-pairs signed rank tests. BSA, body surface area; CT, computed tomography; WA, wall area.

creased significantly in the 4M-benralizumab group (Fig. 2f–h).

We also compared the parameters of CT images before and after benralizumab treatment. The levels of WA/BSA in the third generation decreased, whereas those in the fourth to sixth generations did not change (Fig. 3a–d). The %WA levels in the third and sixth generations were significantly decreased (Fig. 3e–h) and the TAC in the whole lung was significantly increased (Fig. 4).

To elucidate the clinical significance of changes in airway images, we analyzed the correlation between the amount of change in WA% (Δ WA%) in each generation and TAC (Δ TAC), clinical background, and changes in clinical parameters. Correlation between baseline blood eosinophil count and Δ WA% was observed in the third and sixth generations (Fig. 5a–b) and Δ TAC (Fig. 5c). Additionally, Δ TAC correlated with exacerbation reduction rate (Δ exacerbation). Partial correlations be-

Table 4. Correlation of changes in WA and TAC with clinical parameters

Parameter	Δ WA% (3rd)	Δ WA% (4th)	Δ WA% (5th)	Δ WA% (6th)	Δ TAC
Duration	−0.31 (0.34)	0.86 (0.01)*	0.01 (0.97)	0.39 (0.24)	−0.17 (0.61)
%FEV ₁	0.08 (0.82)	−0.16 (0.65)	0.68 (0.03)*	0.15 (0.65)	0.24 (0.47)
Δ %FEV ₁	−0.25 (0.47)	0.15 (0.67)	0.23 (0.49)	−0.28 (0.40)	0.07 (0.84)
ACT	−0.08 (0.83)	−0.15 (0.65)	0.46 (0.15)	0.13 (0.70)	0.19 (0.58)
Δ ACT	0.05 (0.89)	0.25 (0.45)	0.02 (0.95)	−0.10 (0.76)	0.12 (0.72)
FeNO	0.23 (0.50)	0.17 (0.61)	−0.17 (0.62)	0.10 (0.77)	−0.20 (0.56)
Blood eosinophil	0.65 (0.03)*	−0.19 (0.57)	0.08 (0.81)	0.61 (0.05)*	0.69 (0.02)*
Exacerbation	−0.11 (0.76)	0.03 (0.92)	−0.25 (0.45)	0.17 (0.62)	0.38 (0.25)
Δ Exacerbation, %	−0.26 (0.46)	−0.14 (0.69)	−0.43 (0.19)	0.17 (0.63)	0.62 (0.05)*

Data are expressed as r (p value). WA, wall area; TAC, total airway count; %FEV₁, percent forced expiratory volume in 1 s; ACT, Asthma Control Test; FeNO, fraction of exhaled nitric oxide. * Significant correlation between the parameters (* $p < 0.05$).

tween disease duration and baseline %FEV₁ were also noted; however, the clinical significance was unclear (Table 4).

Discussion/Conclusion

In this study, 11 patients with severe eosinophilic asthma were treated with benralizumab. Airway wall thickening and the number of TAC on the CT were evaluated before and after treatment. Our study revealed two major novel findings: (1) benralizumab improved airway wall thickening and increased TAC and (2) the degree of improvement in imaging parameters correlated with the baseline eosinophil count. To the best of our knowledge, this is the first report on the changes in airway wall thickening and TAC in patients treated with benralizumab.

Previous studies reporting improvements in bronchial wall thickening and airway lumen area with biologics interventions include treatments of omalizumab. Tajiri et al. [20] reported an improvement in airway wall thickness and enlargement of the luminal area on CT images as well as a decrease in the number of exacerbations and an increase in peak expiratory flow values after 48 weeks of treatment with omalizumab. In a small open-label study, Hoshino and Ohtawa [21] reported a significant improvement in airway wall thickening and enlargement of the luminal area in the omalizumab-treated group. Both reports mentioned a decrease in FeNO and sputum eosinophil percentages, which may be associated with an improvement in eosinophilic airway inflammation. Furthermore, 1-year treatment of mepolizumab in the study

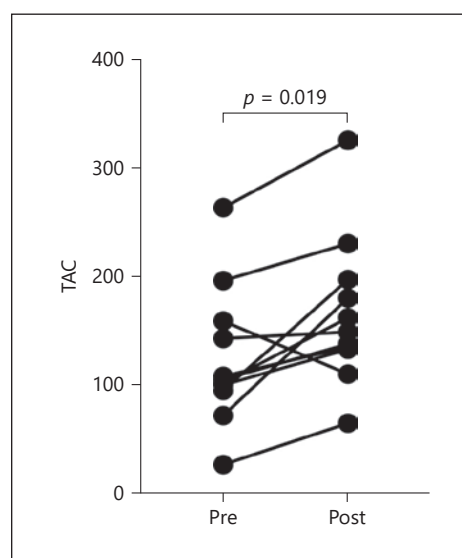


Fig. 4. Changes in TAC with benralizumab treatment. Values were obtained before (“Pre”) and after (“Post”) benralizumab treatment. **a** Right upper lobe. **b** Right middle and lower lobe. **c** Whole right lobe. The p values were calculated via Wilcoxon matched-pairs signed rank tests.

for severe eosinophilic asthma patients revealed the significant improvement of airway wall thickening and airway lumen on CT compared to the placebo group [22]. In the present study, elevated blood eosinophils disappeared in all cases and sputum eosinophils, which were observed in some cases, almost disappeared (data not shown). This suggested that benralizumab properly controlled eosinophilic inflammation in the airways, this effect was reflected in the morphological changes.

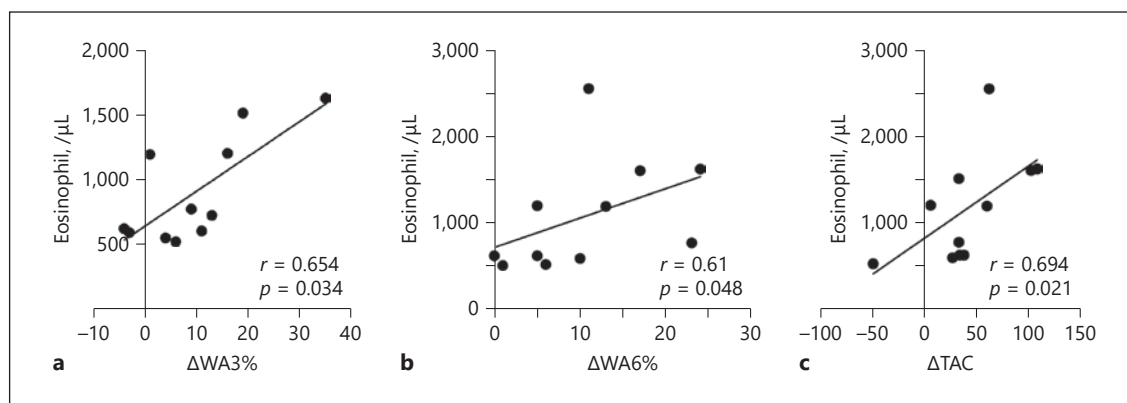


Fig. 5. The correlation between the morphological parameters of CT. Baseline blood eosinophil counts Δ WA3% (a), Δ WA6% (b), and Δ TAC (c). The r and p values were calculated using Spearman's rank analysis. CT, computed tomography; WA, wall area; TAC, total airway count.

In this study, the baseline blood eosinophil count correlated with the changes of imaging features. There was a correlation between the blood eosinophil count and sputum eosinophil percentages [23], especially in severe eosinophilic asthma [24], suggesting that the effects of benralizumab may be reflected in imaging changes in patients with more intense eosinophilic inflammation in the airway. Eosinophils are considered the major source of TGF- β , which is essential for airway remodeling [25]. Moreover, a recent report has also described a mechanism by which eosinophils activated by amphiregulin, an epidermal growth factor family member, produce osteopontin, causing fibrosis of the airways [26]. It can be assumed that the removal of these activated eosinophils from the airways may act in an inhibitory manner on the development of airway remodeling.

Improvement in bronchial wall thickening varied across generations, with a significant improvement observed in the third and sixth generations. However, no change was observed in the other generations. Several reasons can be speculated with this result. One reason is that the image interval in this study might have been short. The omalizumab report mentioned above [20] showed improvement in airway wall thickness and enlargement of the luminal area on the CT after 48 weeks of treatment with omalizumab was similarly evaluated after 16 weeks, with little improvement. Based on these data, a period of around 1 year may be required to evaluate the effect of biologics on airway wall thickening. The second reason is that the partial improvement of the airway may be the clearing of mucus rather than the bronchial wall itself. From the improvement in TAC with the use of benralizumab, it is speculated that mucus plugs and the mucus

attached to the walls of the airways were reduced. It is further speculated that this phenomenon may reduce eosinophil-derived granule proteins such as eosinophil peroxidase in the airways; however, further analysis is needed.

While there are many reports of TAC being correlated with respiratory function in COPD [18, 27], there are only a few reports of TAC being monitored in asthma. Furthermore, its clinical significance remains unclear. Eddy et al. [19] reported that the number of small airways lost correlated with airway wall thickness and airway lumen area in a branching analysis and also correlated with a ventilation defect percentage on a functional magnetic resonance imaging. Although the method of TAC measurement differed slightly in this study, TAC improved in many cases following benralizumab administration. Moreover, it is intriguing to observe that changes in TAC were correlated with changes in the number of exacerbations.

This study had several limitations. First, this was a single-arm study without a controlled comparison and the sample size was small owing to the single-center nature of the study. Second, no patients received the maintenance OCS therapy; this indicates that the study may have targeted less severe cases. Finally, the results of this study showed no correlation between airway wall changes or increased TAC on CT and respiratory function, particularly FEV₁. This indicates that morphological and functional indices are not related. However, it is possible that some of the patients in this study had mild impairments of FEV₁, which may not have been reflected in improvements in FEV₁ despite clinical improvements following the use of biologics. Recently, the association of small airway dysfunction with nocturnal symptoms, airway hyperresponsiveness, and airway inflammation phenotype

has been reported [28–30]. Additionally, it has been reported that methods to analyze small airway dysfunction such as impulse oscillometry are more sensitive than spirometry to biologic treatment effects [31]. Therefore, it is necessary to evaluate small airways in the future.

In summary, we examined the efficacy of benralizumab both clinically and using CT imaging. Eleven patients were studied, and most participants demonstrated an improvement with respect to subjective symptoms and the quality-of-life scores, as well as respiratory function and reduction in exacerbations of asthma. Furthermore, CT imaging analysis showed a decrease in right B¹ airway wall thickness and an increase in the number of bronchi visible on the CT, which could be related to the baseline blood eosinophil count. These data suggest that benralizumab, an anti-IL-5 receptor chain antibody, can greatly reduce airway wall thickening and improve ventilation by clearing an obstructed airway.

Acknowledgments

The authors are grateful for the assistance of Ms. Asako Maruyama (Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan) in managing the clinical data.

Statement of Ethics

This study was conducted in accordance with the ethical principles for medical research involving human subjects, the Declaration of Helsinki, and was approved by the Ethics Committee of the

Niigata University (approval No. 2018-0413). All participants provided written informed consent prior to enrollment.

Conflict of Interest Statement

The authors have no competing interests to declare.

Funding Sources

This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (No. 20K17212).

Author Contributions

Fumito Tsubokawa and Toshiyuki Koya designed the study and wrote the manuscript. Fumito Tsubokawa, Toshiyuki Koya, Yui Murai, Kentaro Tanaka, Yuchi Tsutsui, Shun Naramoto, Natsumi Sakai, Kenjiro Shima, and Yosuke Kimura contributed to data collection. Toshiyuki Koya, Aoki Ami, Satoshi Watanabe, Takashi Hasegawa, and Toshiaki Kikuchi performed the statistical analysis and interpretation of the results. All the authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

- 1 Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA). 2021. Available from: <http://www.ginasthma.org/> (accessed December 15, 2021).
- 2 Niimi A, Matsumoto H, Amitani R, Nakano Y, Mishima M, Minakuchi M, et al. Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. *Am J Respir Crit Care Med*. 2000;162(4 Pt 1):1518–23.
- 3 Krings JG, Goss CW, Lew D, Samant M, McGregor MC, Boomer J, et al. Quantitative CT metrics are associated with longitudinal lung function decline and future asthma exacerbations: results from SARP-3. *J Allergy Clin Immunol*. 2021;148(3):752–62.
- 4 Aysola RS, Hoffman EA, Gierada D, Wenzel S, Cook-Granroth J, Tarsi J, et al. Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. *Chest*. 2008;134(6):1183–91.
- 5 Nishimoto K, Karayama M, Inui N, Mori K, Kono M, Hozumi H, et al. Relationship between fraction of exhaled nitric oxide and airway morphology assessed by three-dimensional CT analysis in asthma. *Sci Rep*. 2017;7(1):10187.
- 6 Gauthier M, Ray A, Wenzel SE. Evolving concepts of asthma. *Am J Respir Crit Care Med*. 2015;192(6):660–8.
- 7 Inoue H, Ito I, Niimi A, Matsumoto H, Matsuo H, Jinnai M, et al. CT-assessed large airway involvement and lung function decline in eosinophilic asthma: the association between induced sputum eosinophil differential counts and airway remodeling. *J Asthma*. 2016;53(9):914–21.
- 8 Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest*. 2018;128(3):997–1009.
- 9 Tang M, Elicker BM, Henry T, Gierada DS, Schiebler ML, Huang BK, et al. Mucus plugs persist in asthma and changes in mucus plugs associate with changes in airflow over time. *Am J Respir Crit Care Med*. 2022;205(9):1036–45.
- 10 FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128–41.

- 11 Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multi-centre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115–27.
- 12 Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448–58.
- 13 Sehmi R, Lim HF, Mukherjee M, Huang C, Radford K, Newbold P, et al. Benralizumab attenuates airway eosinophilia in prednisone-dependent asthma. *J Allergy Clin Immunol*. 2018;141(4):1529–32.e8.
- 14 Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343–73.
- 15 American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171(8):912–30.
- 16 Yasui H, Inui N, Furuhashi K, Nakamura Y, Uto T, Sato J, et al. Multidetector-row computed tomography assessment of adding budesonide/formoterol to tiotropium in patients with chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*. 2013;26(3):336–41.
- 17 Hartley RA, Barker BL, Newby C, Pakkal M, Baldi S, Kajekar R, et al. Relationship between lung function and quantitative computed tomographic parameters of airway remodeling, air trapping, and emphysema in patients with asthma and chronic obstructive pulmonary disease: a single-center study. *J Allergy Clin Immunol*. 2016;137(5):1413–22.e12.
- 18 Tanabe N, Sato S, Oguma T, Shima H, Sato A, Muro S, et al. Associations of airway tree to lung volume ratio on computed tomography with lung function and symptoms in chronic obstructive pulmonary disease. *Respir Res*. 2019;20(1):77.
- 19 Eddy RL, Svenningsen S, Kirby M, Knipping D, McCormack DG, Licskai C, et al. Is computed tomography airway count related to asthma severity and airway structure and function? *Am J Respir Crit Care Med*. 2020;201(8):923–33.
- 20 Tajiri T, Niimi A, Matsumoto H, Ito I, Oguma T, Otsuka K, et al. Comprehensive efficacy of omalizumab for severe refractory asthma: a time-series observational study. *Ann Allergy Asthma Immunol*. 2014;113(4):470–5.e2.
- 21 Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. *Respiration*. 2012;83(6):520–8.
- 22 Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360(10):973–84.
- 23 Schleich FN, Manise M, Sele J, Henket M, Seidel L, Louis R. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. *BMC Pulm Med*. 2013;13:11.
- 24 Yancey SW, Keene ON, Albers FC, Ortega H, Bates S, Bleecker ER, et al. Biomarkers for severe eosinophilic asthma. *J Allergy Clin Immunol*. 2017;140(6):1509–18.
- 25 Kariyawasam HH, Robinson DS. The role of eosinophils in airway tissue remodelling in asthma. *Curr Opin Immunol*. 2007;19(6):681–6.
- 26 Morimoto Y, Hirahara K, Kiuchi M, Wada T, Ichikawa T, Kanno T, et al. Amphiregulin-producing pathogenic memory T helper 2 cells instruct eosinophils to secrete osteopontin and facilitate airway fibrosis. *Immunity*. 2018;49(1):134–50.e6.
- 27 Kirby M, Tanabe N, Tan WC, Zhou G, Obeidat M, Hague CJ, et al. Total airway count on computed tomography and the risk of chronic obstructive pulmonary disease progression. Findings from a population-based study. *Am J Respir Crit Care Med*. 2018;197(1):56–65.
- 28 van der Wiel E, Postma DS, van der Molen T, Schiphof-Godart L, Ten Hacken NHT, van den Berge M. Effects of small airway dysfunction on the clinical expression of asthma: a focus on asthma symptoms and bronchial hyper-responsiveness. *Allergy*. 2014;69(12):1681–8.
- 29 Abdo M, Trinkmann F, Kirsten AM, Biller H, Pedersen F, Waschki B, et al. The relevance of small airway dysfunction in asthma with nocturnal symptoms. *J Asthma Allergy*. 2021;14:897–905.
- 30 Abdo M, Pedersen F, Kirsten AM, Veith V, Biller H, Trinkmann F, et al. Longitudinal impact of sputum inflammatory phenotypes on small airway dysfunction and disease outcomes in asthma. *J Allergy Clin Immunol Pract*. 2022;10(6):1545–53.e2.
- 31 Abdo M, Watz H, Veith V, Kirsten AM, Biller H, Pedersen F, et al. Small airway dysfunction as predictor and marker for clinical response to biological therapy in severe eosinophilic asthma: a longitudinal observational study. *Respir Res*. 2020;21(1):278.