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RESEARCH ARTICLE

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Efficacy and safety of benralizumab in elderly patients with severe eosinophilic asthma

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ABSTRACT

Background: Biologics are the important drugs for severe asthma, but clinical trials included few elderly patients. Data on the safety and efficacy of benralizumab in elderly asthma patients are limited.

Methods: This clinical study was a multicentre, retrospective, observational study at two hospitals. Patients aged ≥18 years diagnosed with severe asthma treated with benralizumab were included. Elderly patients were defined as those aged 70 years or older. Efficacy and safety were then analyzed in elderly and non-elderly patients. The primary endpoints were the annual number of asthma exacerbations for efficacy and the discontinuation rate due to adverse events for safety.

Results: Between August 2016 and October 2022, 61 patients were enrolled; 10 patients were excluded, and 51 (22 elderly, 29 non-elderly) patients were analyzed. In elderly patients, the annual number of asthma exacerbations before treatment with benralizumab (pre-benralizumab) was 3.78, and the number during treatment with benralizumab was 1.26, a decrease of 2.52 (95% confidence interval [CI], 1.3 to 3.74, $p < 0.001$). In non-elderly patients, the annual number of asthma exacerbation in the pre-benralizumab period was 3.24, and during treatment with benralizumab it was 0.68, a decrease of 2.56 (95% CI, 1.3 to 3.82, $p < 0.001$). There was no significant difference in discontinuation due to treatment-related adverse events (elderly vs non-elderly, 2 (9%) vs 0 (0%), $p = 0.18$).

Conclusion: Benralizumab reduced the annual number of asthma exacerbations and was well tolerated in elderly patients.

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KEYWORDS
Asthma; adverse event; benralizumab; biologics; elderly patients

Introduction

Asthma is characterized by chronic airway inflammation and affects 260 million people worldwide [1]. The mean prevalence of asthma in adults is 6–10% of adults [2], with 5–10% of them having severe asthma [3], which results in lower quality of life, higher medical costs, and higher mortality [2,4]. Biologics are the important drugs for severe asthma. Of them, benralizumab, an IL-5 receptor antagonist, is effective in severe eosinophilic asthma. In a Phase III, randomized, clinical trial, benralizumab reduced the annual asthma exacerbation rate [5,6] and the dose of oral corticosteroids (OCS) [7,8].

On the other hand, with the aging of population, treatment and care of elderly asthma patients is getting attention. Asthma in elderly patients is often characterized by difficulties in diagnosis and treatment due to smoking, comorbidities, polypharmacy, and age-related changes. Asthma in elderly patients is classified by the time of onset into long-standing asthma, recurrent asthma that remitted in childhood, and late-onset asthma [9–11]. Late-onset asthma in particular accounts for a large proportion of cases in elderly asthma patients, and several combinations with type-2 and non-type-2 immunity result in difficult treatment [9].

However, data on the safety and efficacy of benralizumab in elderly asthma patients are limited. Principe et al. reported a meta-analysis of randomized, clinical

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trials, and they found that age did not negatively affect the efficacy of benralizumab [12]. However, asthma patients suitable for clinical trials are quite different from real-world asthma patients [13]. A significant number of asthma patients in real-world settings do not meet the criteria of clinical trials for airflow obstruction, bronchodilator reversibility, smoking history, age, comorbidities and so on [13,14]. It has been said that only about 20–30% of asthma patients seen in clinical practice are eligible for clinical trials. Meta analysis of biologics in severe asthma with real-world settings showed reduced exacerbation and improved lung function [15]. But real-world data for the treatment of severe asthma in elderly patients are limited so more studies are needed.

Recently, Valverde-Monge M et al. reported safety and efficacy of benralizumab in elderly asthma patients with retrospective setting [16]. But the number of elderly subjects is relatively small and they could not show the OCS reduction with benralizumab in elderly asthma patients. Further study is needed to evaluate the safety and efficacy of biologics in elderly asthma patients. Therefore, the safety and efficacy of benralizumab were evaluated in elderly asthma patients in a real-world setting in our hospitals.

Patients and methods

Study design and participants

This was a multi-centre, retrospective, observational study in Yokohama City University Hospital and Yokohama City University Medical Center, Yokohama, Japan. Patients aged ≥18 years diagnosed with severe asthma treated with benralizumab between August 2016 and October 2022 were included. Severe asthma was defined according to the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines [17] i.e. all patients had been treated with high-dose inhaled corticosteroids (ICS) plus at least one additional controller: long-acting bronchodilator antagonist (LABA), leukotriene modifier (LTRA), theophylline (SRT), or continuous OCS over 6 months, or a biologic. In Japan, patients with uncontrolled asthma even with high-dose inhaled steroids and other long-term control medications are eligible for benralizumab. The elderly patients were defined as those aged 70 years or older, as in a previous study [18]. Eosinophilic asthma was defined as asthma with a peripheral eosinophil level >300 cells/μl before asthma treatment or the start of benralizumab. We made the diagnosis of concomitant of COPD in asthma with post-bronchodilator forced expiratory volume in 1 s ($FEV_{1.0}$)/forced vital capacity (FVC) ratio ($FEV_{1.0\%}$) <0.7 and smoking history of ≥10 pack-year in ≥40-year-old subjects based on previous studies [19,20]. This study was approved by the institutional review board of Yokohama City University Hospital (approval date: 12 January 2023, approval no. F221100030) and Yokohama City University Medical Center (approval date: 12 January 2023, approval no. F230400031). Due to the retrospective nature of this study, the need to obtain written, informed consent was waived by the institutional review board of Yokohama City University Hospital. Patient anonymity was preserved using methods approved by the Ethics Committee. All methods were carried out in accordance with relevant guidelines and regulations.

Procedures

Benralizumab 30 mg was given subcutaneously at the initial visit, at 4 weeks, at 8 weeks, and at 8-week intervals thereafter. Age, sex, height, weight, smoking history, complications and comorbidities, and age of onset of asthma were collected from electronic medical records for all patients. The peripheral eosinophil level, serum total immunoglobulin E level, and specific immunoglobulin E level (RAST) were collected prior to administration of benralizumab and one year after starting benralizumab. RAST-positive was defined by inhaled antigens such as house dust, mite, pollens (Japanese cedar, cypress, alder, birch, chamogoya, Japanese mugwort, ragweed, mugwort), cockroach, dander (cat, dog), or mold spores (Alternaria, Cladosporium [Hormodendrum], Malassezia, Candida, Aspergillus, Penicillium) [21]. FVC, $FEV_{1.0}$, and $FEV_{1.0\%}$ were obtained prior to administration of benralizumab and one year after starting benralizumab. If patients discontinued benralizumab, laboratory data and spirometry were collected only during administration of benralizumab.

Outcome

The primary endpoints were the annual number of asthma exacerbations for efficacy and the discontinuation rate due to adverse events for safety. The annual number of exacerbations was calculated by the number of exacerbations × 365/total duration of follow-up. An exacerbation was defined as a worsening of asthma that led to one of the following: use of systemic corticosteroids; temporary increase in maintenance oral corticosteroids; visit to emergency department due to asthma exacerbation that needed systemic corticosteroids; or hospitalized for asthma exacerbation.

Secondary endpoints were interval change of spirometry and OCS reduction calculated as the equivalent dose of prednisolone for efficacy from baseline to 24 weeks (6 months) after the start of benralizumab.

Statistical analysis

All statistical analyses were performed with EZR [22], which is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Comparisons were made using *t*-tests, the Mann-Whitney *U* test, the paired-sample *t*-test, or the Wilcoxon signed-rank test, as appropriate, for continuous variables. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test. Significance was set as values of $p < 0.05$, and all tests were two-tailed.

Results

Patients' characteristics

Between August 2016 and October 2022, 61 patients were enrolled. Ten patients were excluded (4 patients were lost to follow up, 4 patients started benralizumab at another hospital, 2 patients had their diagnoses changed during benralizumab treatment, with 1 diagnosed with EGPA and the other diagnosed with ABPM, and their treatments were changed). Thus, 51 patients were included in the analysis (Figure 1).

The patients' baseline characteristic are shown in Table 1. A total of 22 patients were elderly patients, with a median age of 75 (71–86) years, and 29 patients were non-elderly patients, with a median age of 56 (22–68) years. Of the elderly patients, 12 (55%) were past smokers, and 10 (45%) were never smokers. Of the non-elderly

Table 1. Patients' characteristics.

	Elderly patients ($n = 22$)	Non-elderly patients ($n = 29$)	*p*-value
Age (y)	75[71–86]	56 [22-68]	
Sex			
Male	8 (36)	11 (28)	1
Female	14 (64)	18 (72)	
Smoking history (Current/past/never)	0/12/10	0/15/14	1
Pack-years of smoking	28.1(±30.1)	22.8 (±23.1)	0.61
BMI (kg/m^2)	24.6 (±3.7)	25.2 (±5.7)	0.73
Onset of asthma (y)	50.3 (±17.8)	27.8 (±16.1)	<0.001
Duration of benralizumab injections (days)	777 (±611)	894 (±509)	0.46
Complication and comorbidity			
Chronic obstructive pulmonary disease	14 (64)	6 (21)	0.003
Allergic rhinitis	10 (45)	11 (38)	0.77
Eosinophilic sinusitis	3 (14)	10 (34)	0.11
Sinusitis	1 (4.5)	2 (7)	1
Eosinophilic otitis media	2 (9.1)	4 (14)	0.69
Aspirin exacerbated respiratory disease	2 (9.1)	2 (7)	1
Allergic bronchopulmonary mycosis	2 (9.1)	1 (3.5)	0.57
Chronic eosinophilic pneumonia	1 (4.5)	3 (10)	0.63
Hypereosinophilic syndrome	1 (4.5)	0	0.43
Eosinophilic granulomatosis with polyangiitis	1 (4.5)	5 (17.5)	0.22
Eosinophilic gastroenteritis	0	1 (3.5)	1
Treatment			
ICS	22 (100)	29 (100)	1
LABA	22 (100)	28 (97)	1
LAMA	11 (50)	17 (59)	0.58
LTRA	15 (68)	18 (62)	0.77
SRT	6 (27)	12 (41)	0.38
Oral glucocorticoids	8 (36)	13 (45)	0.44
Prior biologic use (omalizumab/mepolizumab/dupilumab)	1/4/0	0/4/2	0.45
Spirometry	n = 18	n = 22	
FVC (mL)	2818(±856)	2971(±889)	0.63
$FEV_{1.0}$ (mL)	1469 (±475)	1797 (±630)	0.088
$\%FEV_{1.0}$ (%)	63.6 (±18.7)	80.5 (±17.6)	0.012
$FEV_{1.0\%}$ (%)	50.4 (±14.3)	64.6 (±15.8)	0.013
Blood test	n = 12	n = 28	
Peripheral eosinophil level (/μl)	228 (±309)	338 (±344)	0.3
Serum total IgE level (IU/mL)	472 (±339)	732 (±1268)	0.32
Serum radioallergosorbent test (positive/negative/unknown)	(10/8/4)	(15/4/10)	0.17

Date are means (±SD), numbers (%), or medians [range].
BMI, body mass index; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SRT, sustained release theophylline; ABPM, allergic bronchopulmonary mycosis; CEP, chronic eosinophilic pneumonia; HES, hypereosinophilic syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; EGE, eosinophilic gastroenteritis.

patients, 15 (52%) were past smokers, and 14 (48%) were never smokers. There were no current smokers in either group. The age of asthma onset was 50.3 ± 17.8 years in elderly patients and 27.8 ± 16.1 years in non-elderly patients.

Comorbidities and complications are shown in Table 1. Of the elderly patients, 14 (64%) were diagnosed with chronic obstructive pulmonary disease (COPD), 10 (45%) were diagnosed with allergic rhinitis, 3 (14%) were diagnosed with eosinophilic sinusitis (All subjects had nasal polyposis), and 2 (9.1%) were diagnosed with eosinophilic otitis media. The percentage of COPD patients was higher in the elderly group than in the non-elderly group.

All patients were treated with ICS. Of the elderly patients, 22 (100%) were treated with LABA, 11 (50%) with LAMA, 15 (68%) with LTRA, 6 (27%) with SRT, and 8 (36%) with OCS.

Biologics were used in 5 (23%) elderly patients (omalizumab in 1 and mepolizumab in 4). All those 5 subjects switched to benralizumab from other biologics. No significant differences in treatment prior to benralizumab were seen between elderly and non-elderly patients.

%$FEV_{1.0}$ was 63.6 (±18.7) % in elderly patients and 80.5 (±17.6) % in non-elderly patients, $FEV_{1.0\%}$ was 50.4 (±14.3) % in elderly patients and 64.6 (±15.8) % in non-elderly patients; elderly patients had a lower %$FEV_{1.0}$ and $FEV_{1.0\%}$ than non-elderly patients ($p = 0.012$, $p = 0.013$ respectively). The peripheral eosinophil level, serum total IgE level, and RAST showed no significant differences between elderly and non-elderly patients.

Primary efficacy endpoint

In elderly patients, the annual number of asthma exacerbations was 3.78 before treatment with benralizumab (pre-benralizumab) and 1.26 during treatment with benralizumab, showing a decrease of 2.52 (95% confidence interval [CI], 1.3 to 3.74, $p < 0.001$). In non-elderly patients, the annual number of asthma exacerbations was 3.24 pre-benralizumab and 0.68 during benralizumab, a decrease of 2.56 (95% CI, 1.30 to 3.82, $p < 0.001$) (Figure 2). There was no statistically significant difference between elderly and non-elderly asthma patients in the reduction of the number of exacerbations (95% CI, −1.80 to 1.71, $p = 0.96$).

Secondary efficacy endpoint

Interval changes of spirometry are shown in Figure 3. The interval change of $FEV_{1.0}$ was 102 ml ($p = 0.06$) in elderly patients and 50 ml ($p = 0.56$) in non-elderly patients. FVC was −75 ml ($p = 0.41$) and 105 ml, respectively ($p = 0.08$). There was no statistically

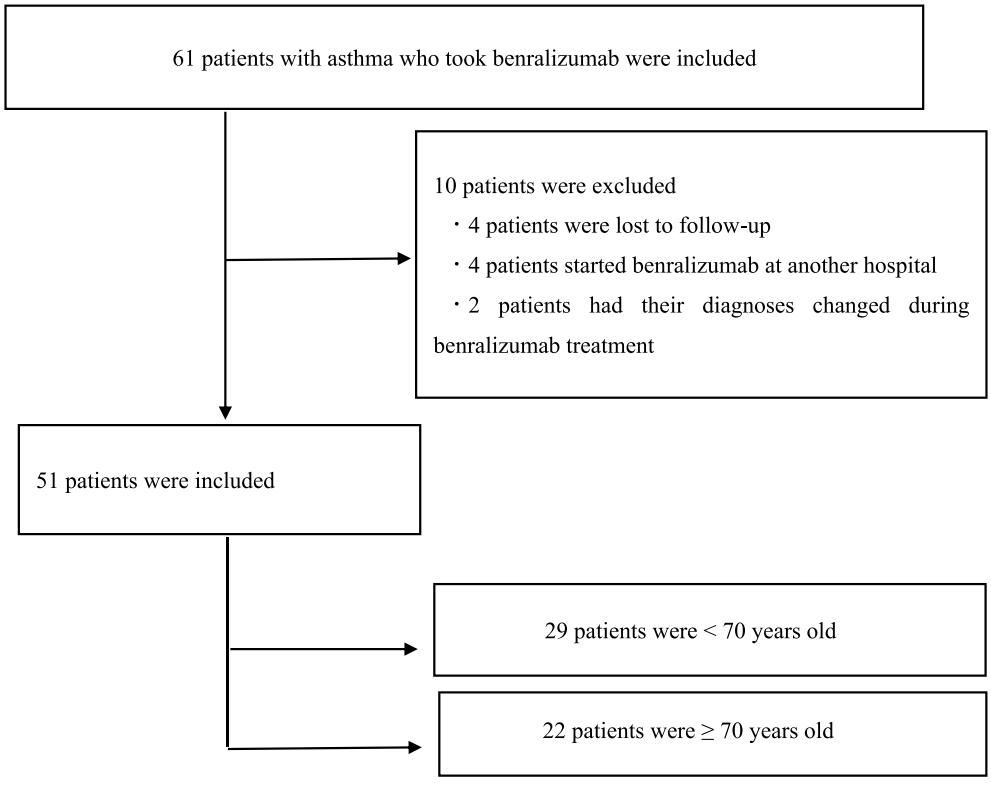

Figure 1. Flow diagram of patient selection.

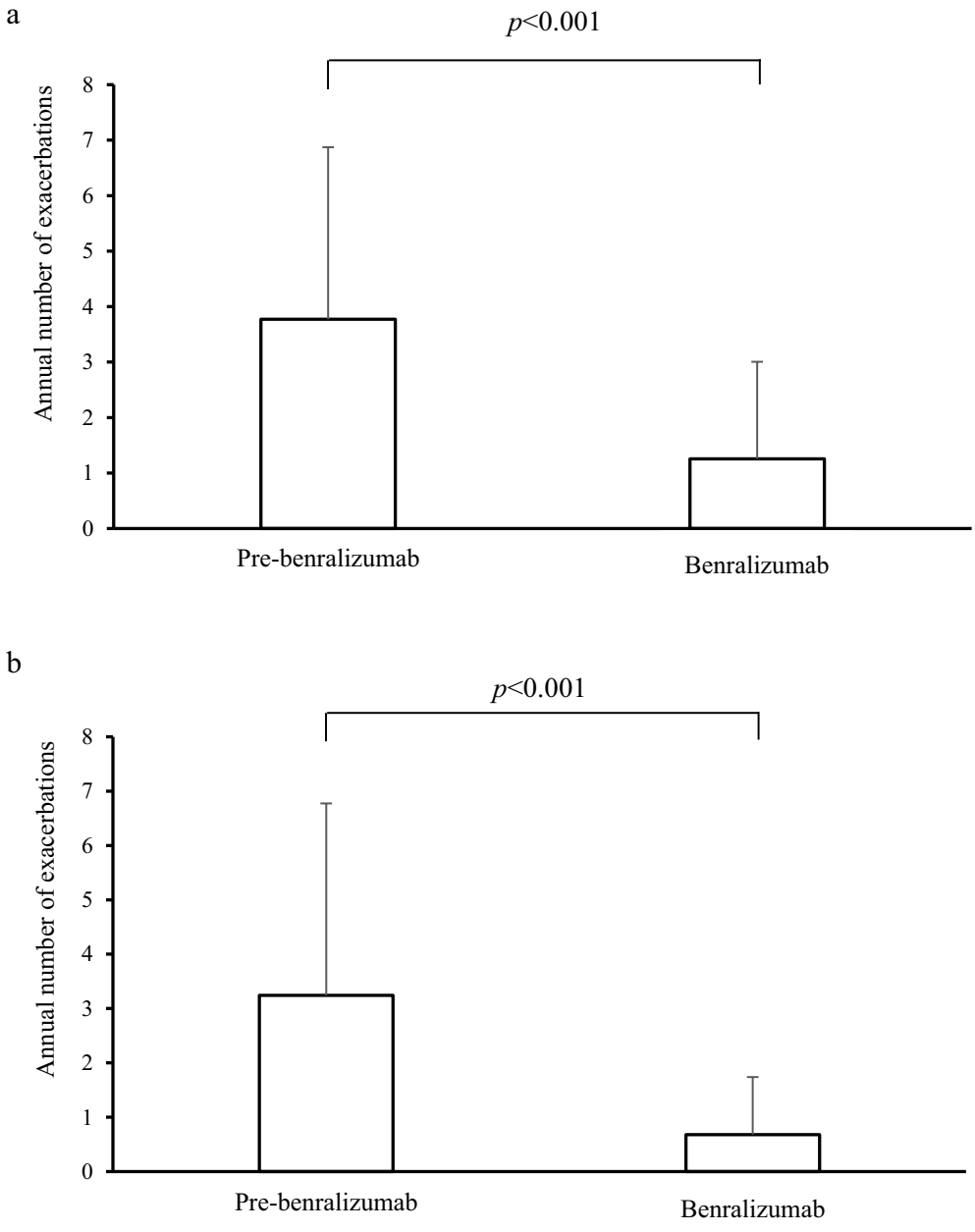

Figure 2. Effectiveness of benralizumab by group.

The annual number of exacerbations is improved with benralizumab in both elderly patients (A) and non-elderly patients (B).

significant difference between elderly and non-elderly asthma patients in change of $FEV_{1.0}$ ($p = 0.58$) and FVC ($p = 0.16$). Reductions in the dose of OCS between baseline before starting benralizumab (Baseline) and 6 months later (6 M) are shown in Figure 4. The OCS dose was 5 [1.5–20] mg at baseline and 4 [0–5] mg ($p = 0.06$) at 6 M in elderly patients ($n = 8$), and 7 [3-30] mg at baseline and 5 [0–9] mg ($p = 0.024$) at 6 M in non-elderly patients ($n = 13$). There was no statistically significant difference between elderly and non-elderly asthma patients in reduction of the OCS dose ($p = 0.91$).

Safety

Adverse events occurring during treatment with benralizumab are shown in Table 2. Overall, 9 of 22 elderly patients and 10 of 29 non-elderly patients discontinued benralizumab. Benralizumab was discontinued due to any treatment-related adverse events in 2 (9%) elderly patients and no non-elderly patients, with no significant difference in discontinuation due to treatment-related adverse events. Pharyngalgia hoarseness, and fatigue were treatment-related reasons for discontinuation. Two elderly patients died during benralizumab therapy, one of chronic heart

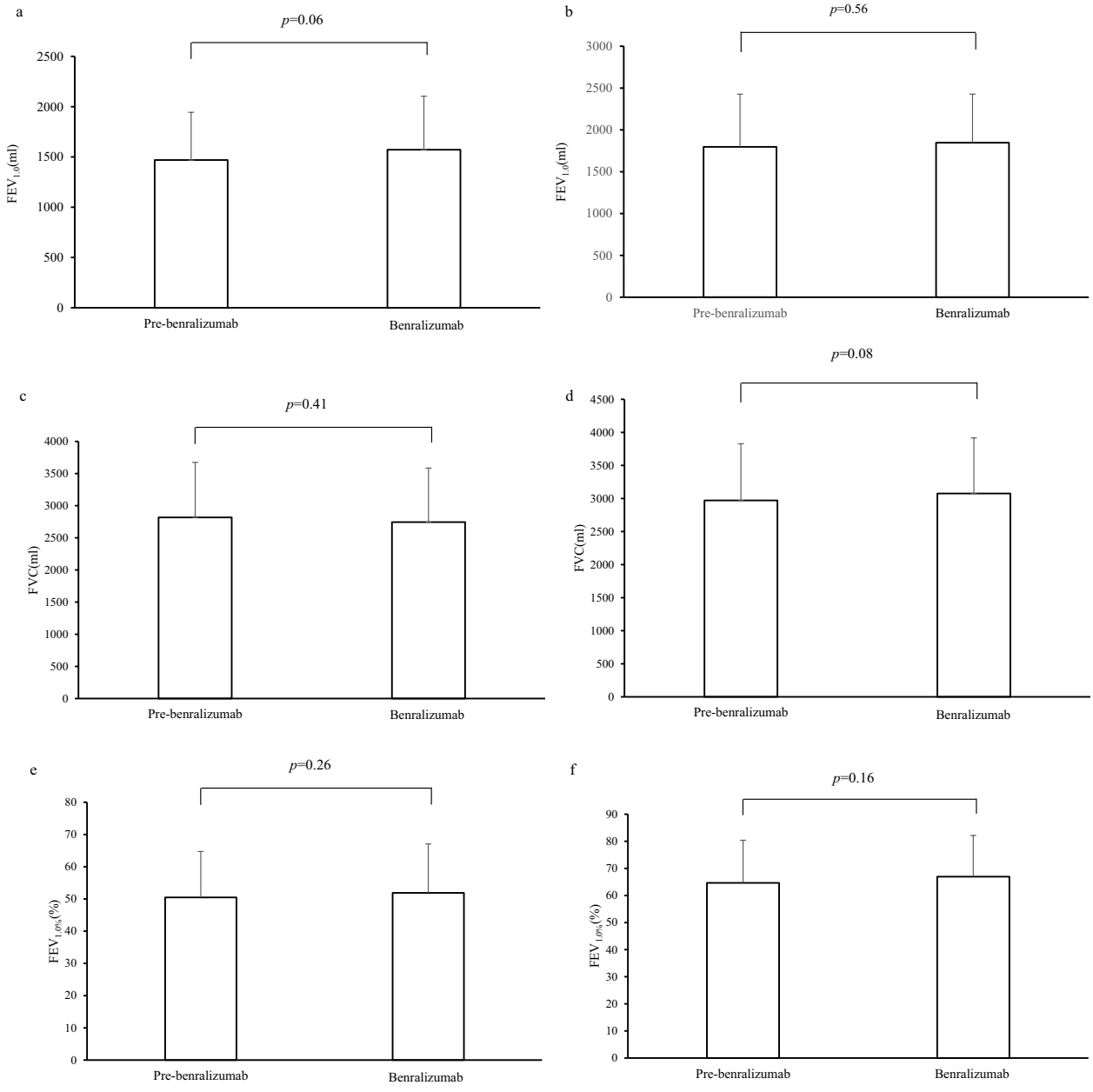

Figure 3. Interval changes of spirometry with benralizumab.

$FEV_{1.0}$ does not improve with benralizumab in both elderly patients (A) and non-elderly patients (B). FVC does not improve with benralizumab in both elderly patients (C) and non-elderly patients (D). $FEV_{1.0\%}$does not improve with benralizumab in either elderly patients (E) or non-elderly patients (F).

failure and the other of non-occlusive mesenteric ischemia; both deaths were unrelated to benralizumab.

The reasons for the discontinuation of benralizumab in the remaining 5 elderly asthma patients were as follows: 2 due to worsening of asthma control, 1 due to financial reasons, 1 due to worsening eosinophilic sinusitis, and 1 due to treatment interruption caused by decreased ADL resulting from aspiration pneumonia. The reasons for the discontinuation of benralizumab in the remaining 10 non-elderly asthma patients were as follows: 5 due to worsening of asthma control, 2 due to worsening eosinophilic otitis media, 1 due to worsening EGPA, 1 due to pregnancy, and 1 due to financial reasons.

Discussion

In the present study, benralizumab reduced the annual number of asthma exacerbations without increasing the discontinuation rate due to adverse events in elderly patients.

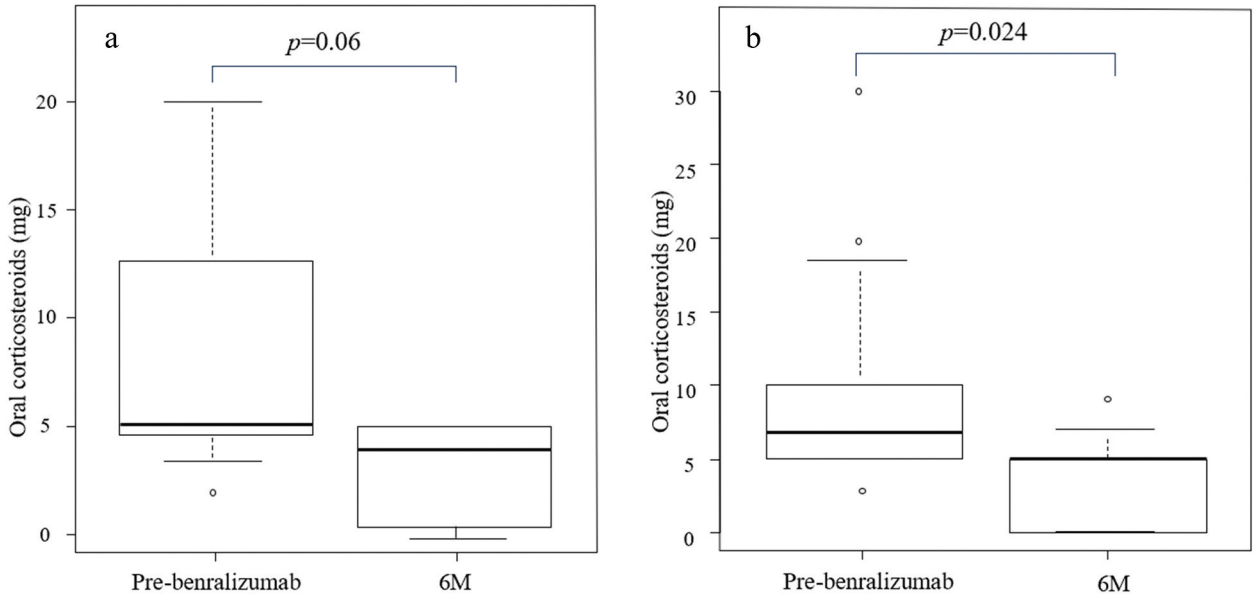

Figure 4. OCS dose reduction from baseline.

OCS dose reduction from baseline before the start of benralizumab (pre-benralizumab) to 6 months after the start of benralizumab (6 M). (A) shows elderly patients ($n = 8$) ($p = 0.06$), and (B) shows non-elderly patients($n = 13$) ($p = 0.024$). The OCS dose is not significantly decreased in elderly patients, but it is decreased in non-elderly patients.

Table 2. Adverse events during treatment with benralizumab.

	Elderly patients ($N = 22$)	Non-elderly patients ($N = 29$)	p-value
Any events leading to treatment discontinuation	9 (41)	10 (34)	0.77
Any treatment-related adverse event leading to treatment discontinuation	2 (9)	0	0.18
Pharyngalgia, hoarseness	1 (4.5)	0	0.43
Fatigue	1 (4.5)	0	0.43

In this study, benralizumab reduced exacerbation, which was not significantly different between elderly and non-elderly asthma subjects. Exacerbation of asthma increases several risks, such as hospitalization and OCS bursts. Elderly asthma patients' hospitalization increased delirium and death due to delirium [23], and OCS bursts as treatment of asthma exacerbations increased adverse events (gastrointestinal bleeding, sepsis, heart failure, etc.), regardless of duration of OCS use [24,25], decreasing the number of asthma exacerbations is thus very important.

Interval changes of $FEV_{1.0}$ did not improve in both groups. Previous studies showed that the biomarker for benralizumab is type-2 inflammation, with, for example, peripheral eosinophil levels over 300/μl. The presence of non-type-2 inflammation with smoking or obesity might hinder the effect of benralizumab [26]. Some patients with a smoking history, asthma COPD overlap syndrome (ACO), and obesity were included in the present study. Benralizumab is less effective in COPD than in asthma [27], since it caused less $FEV_{1.0}$ improvement.

The usual OCS dose was not decreased in elderly asthma patients after the start of benralizumab. However, in non-elderly patients, the usual OCS dose was decreased. In elderly patients, more ACO patients were included than in non-elderly patients. This could be the cause of the decrease in OCS reduction. It might also be difficult to see a significant difference with the small number of elderly asthma patients taking regular OCS in this study.

Nine elderly patients discontinued benralizumab, with two due to treatment-related adverse events; no non-elderly patients discontinued benralizumab (Table 2). Compared with previous studies, discontinuation due to treatment-related adverse events appeared to have a high incidence. One patient discontinued benralizumab due to pharyngalgia and hoarseness. Although not considered a serious adverse event, even minor symptoms may result in discontinuation in elderly patients. The results are limited by the small number of elderly patients, although differences were not significant.

In the present study, late-onset asthma was more common in elderly patients. Age-related changes in the immune response, immunosenescence, contribute to late-onset asthma. Such changes include

proinflammatory mediator production, functional declines in phagocytosis and antigen presentation, and so on. Although immunosenescence has important consequences in elderly asthma patients, knowledge about immunosenescence in asthma is limited. Further study is needed to determine whether the effect of biologics could be altered by immunosenescence.

The present study had several limitations. First, this was a retrospective study with a small number of patients. Especially, the number of asthma subjects taking maintenance OCS was very small. Therefore, we included all the subjects who met the inclusion criteria during the study period without power-calculation. Several results that did not reach statistical significance may have type II errors. Second, this was a retrospective study and there were no predefined diagnostic criteria for asthma and schedule of laboratory test in this study. Therefore, it is difficult to add reversibility and PD20 results. But all subjects were diagnosed by board-certified pulmonologists and/or allergists based on clinical and laboratory findings. It was also impossible to evaluate patient-reported symptom scores such as the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ), as well as fractional exhaled nitric oxide.

Conclusion

In conclusion, the present real-world study suggests that benralizumab is safe and effective in elderly asthma patients. Further study is needed to confirm our findings.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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