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Efficacy and safety of baricitinib in rheumatoid arthritis patients with moderate renal impairment: a multicenter propensity score matching study

Akira Maeyama[1*], Masakazu Kondo[2], Hiroshi Harada[3], Eisuke Shono[4], Ryuji Nagamine[5], Tomomi Tsuru[6], Yasushi Inoue[7], Munetoshi Nakashima[8], Yutaro Yamasaki[1], Hiroaki Niiro[9], Yasuharu Nakashima[10] and Takuaki Yamamoto[1]

Abstract

Background This study aimed to compare the efficacy and safety of baricitinib in patients with rheumatoid arthritis (RA) receiving different doses based on renal function.

Methods We conducted a retrospective study within the JAK Study Group, involving 23 facilities in Fukuoka Prefecture, examining patients treated with baricitinib for RA. Patients were categorized into two dose groups: 4 mg with normal/mild renal dysfunction and 2 mg with moderate renal dysfunction. Baricitinib's efficacy, retention rate, and safety were compared between the groups after propensity score matching.

Results After propensity score matching, disease duration, methotrexate dosage, and anti-cyclic citrullinated peptide antibody positivity rate were balanced across 33 patients in both groups. No significant differences were observed between the groups in tender/swollen joint counts, changes in evaluator/patient global assessments, achievement rate of low disease activity, remission rate on clinical/simplified disease activity indices, or retention rate. Additionally, the incidence of adverse events aligned with previous reports, indicating similar drug safety profiles.

Conclusions Baricitinib 2 mg in RA patients with moderate renal dysfunction showed comparable efficacy and retention rate to 4 mg in patients with normal/mild renal dysfunction. The incidence and types of adverse events were consistent with previous studies, indicating the safety of the drug at these dosages.

Keywords Baricitinib, JAK inhibitor, Japan, Propensity score matching, Rheumatoid arthritis

*Correspondence:
Akira Maeyama
akira.maeyama0713@joy.ocn.ne.jp

Full list of author information is available at the end of the article

Background

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by joint inflammation and various complications [1]. Irreversible structural damage to the joints can develop as inflammation progresses, resulting in functional impairment. Therefore, active therapeutic intervention and remission from the early stages of onset are necessary based on the concept of "Treat to Target" [2–4]. Currently, RA treatment is progressing rapidly with the advent of biologics and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) in addition to conventional disease-modified antirheumatic drugs (DMARDs) [5].

The most common age of RA onset was in the 40s. However, with the advancing age of patients with RA in Japan and more effective treatments allowing patients to live longer, cases of elderly-onset RA has been increasingly reported [67]. The rising number of elderly patients with RA and its associated complications pose a significant health challenge for RA treatment in Japan [8]. In addition, RA often progresses to chronic kidney disease, and a decreased estimated glomerular filtration rate (eGFR) has been observed in RA patients [9]. This is an important clinical challenge because decreased renal function limits treatment options for this disease [10]. RA has also been reported to impair renal function [11]. In addition to Methotrexate (MTX) and biologic disease-modifying anti-rheumatic drugs (bDMARDs), Janus kinase (JAK) inhibitors are also being increasingly used to treat aging RA patients.

The oral drug baricitinib is a Janus kinase (JAK) inhibitor that selectively blocks JAK1 and JAK2 [12–14] and is indicated for the treatment of RA and atopic dermatitis, as approved by the US Food and Drug Administration (FDA), European Medicines Agency [15], and Japan. Baricitinib is a renally excreted drug with an optimal dose of 4 mg; however, in cases of moderate renal dysfunction, the maximum concentration (Cmax) and the area under the curve (AUC) in the blood are approximately 50% and 2 fold higher, respectively, compared to those with normal renal function or mild renal dysfunction. Since clinical safety events are often linked to Cmax and a dosing regimen change cannot adequately address the elevated Cmax, dose reduction is a more effective strategy. Therefore, an optimal dose of 2 mg is recommended for patients with moderate renal dysfunction [15], and is commonly used in real-world settings in Japan.

Although two major clinical trials, the RA-BUILD and BEACON studies, have reported the efficacy and safety of baricitinib 2 mg [16, 17], there have been no studies on the clinical efficacy and safety of baricitinib 2 mg in patients with RA and moderate renal dysfunction. We hypothesized that administering a 2 mg dose of baricitinib to patients with impaired renal function would yield safety and efficacy outcomes comparable to those observed with a 4 mg dose in patients with normal renal function. Therefore, this study aimed to evaluate the safety and efficacy of baricitinib, by comparing patients with normal renal function or mild renal impairment receiving a 4 mg dose to those with moderate renal impairment receiving a 2 mg dose.

Methods

Study design

This retrospective study was conducted using a multicenter registry of patients with RA. The Fukuoka JAK Registry was created by 23 medical institutions in Fukuoka Prefecture, Japan, and consists of a multicenter cohort of patients with RA treated with biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs). RA was diagnosed based on the 1987 American College of Rheumatology (ACR) [18] or 2010 ACR/European League Against Rheumatism (EULAR) criteria [19]. Patients with RA who started baricitinib treatment between September 2017 and February 2021 and were followed up for more than 52 weeks were included in this study. The patients were followed up at 4, 12, 24, and 52 weeks after the start of treatment. Patients who received non-optimal treatment (i.e., patients with normal renal function or mild renal impairment receiving a 2 mg dose, or those with moderate renal impairment receiving a 4 mg dose) were excluded from the analysis.

Data extraction

For the patients' baseline characteristics and disease characteristics, the following were extracted from the Fukuoka JAK Registry: age, sex, height, weight, body mass index (BMI), disease duration, Steinbrocker stage, Steinbrocker class, anti-citrullinated protein antibody (ACPA) titer, rheumatoid factor, tender joint count (out of 28 joints, TJC28), swollen joint count (out of 28 joints, SJC28), evaluator global assessment (EGA), patient global assessment (PGA), previous b/tsDMARD use, concomitant use and doses of MTX and doses of steroids, serum C-reactive protein (CRP), and eGFR.

The following outcomes were evaluated: retention rate, low disease activity, remission rate on the clinical disease activity index (CDAI), simplified disease activity index (SDAI), and adverse events. If treatment was discontinued before one year had elapsed, data were also collected regarding the date and reason for treatment discontinuation.

Ethics and consent statements

This study was conducted with the approval of the Ethics Review Committee (Haradoi Hospital Ethical Review Board: Approval No. 2019006). This study is a multicenter study. In addition, Haradoi Hospital was the

institute of the Ethical Review Committee decided by the Kondo Clinic of Rheumatology and Orthopaedic Surgery, the lead institution of the study. All the patients provided informed verbal consent to participate in this study. The procedure of obtaining informed verbal consent was approved by Haradoi Hospital Ethical Review Board.

Statistical analysis

Patients with missing values for categorical variables were treated as non-responders. Data on continuous variables were imputed using the last observation carried forward method and cases with doses appropriate for renal function were extracted. Patients were divided into two groups: one group of patients who received 4 mg of baricitinib when their eGFR was 60 mL/min/1.73 m [2] or more, and the other group of patients who received 2 mg of baricitinib when their eGFR was 30 mL/min/1.73 m [2] or more but less than 60 mL/min/1.73 m [2].

Patients' baseline characteristics were compared between the 2 mg group and 4 mg groups, and the groups were adjusted using propensity score matching based on the baseline characteristics that differed between them. Baseline characteristics and outcomes were also compared between the groups after matching to verify that they were adequately matched.

Safety outcomes were assessed in terms of the frequency and type of adverse events in the overall (unmatched) group during follow-up. The efficacy outcomes (TJC, SJC, EGA, PGA, CDAI, and SDAI) at the final follow-up; mean changes in TJC, SJC, EGA, and PGA; achievement rate of low disease activity; remission rate on CDAI and SDAI; and retention rate at each time point were compared between the matched 2 mg and 4 mg groups. The retention rate was calculated using the Kaplan-Meier method. The two groups were compared using a two-sided t-test for comparison of mean values and a chi-square test for proportions. A log-rank test was used to compare the retention rates of the 2 mm and 4 mm baricitinib doses. A value of $p \leq 0.05$ was regarded as significant in all cases. Statistical analyses were performed using the SPSS software (version 24.0, IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 170 participants were enrolled in the study (Table 1). Baricitinib was administered at doses of 2 mg and 4 mg to 68 and 102 patients, respectively. There were no cases in which the dose was changed during the follow-up period. The cohort comprised 143 women and 27 men, with a mean age of 61 ± 14.6 years, mean BMI of 23.1 ± 3.59 kg/m^2, and mean disease duration of 15.2 ± 10.3 years.

Baricitinib was administered at optimal dosages in 139 of the 170 patients; 53 patients with moderate renal dysfunction received a dose of 2 mg and 86 patients with normal renal function or mild dysfunction received a dose of 4 mg. Thirty-one patients received non-optimal

Table 1 Baseline characteristics of all participants ($n = 170$). Data are summarized as mean ± SD or count (%)

Baricitinib dosage	2 mg, 68 cases; 4 mg, 102 cases
Age (years)	61.0 ± 14.6
Sex	143 (84.1%) women; 27 (25.9%) men
Height (cm)	156.1 ± 8.7
Weight (kg)	56.5 ± 10.8
BMI (kg/m^2)	23.1 ± 3.59
Disease duration (years)	15.2 ± 10.3
Steinbroker stage (1/2/3/4)	30/60/27/53
Steinbroker class (1/2/3/4)	48/99/20/3
Tender joint count (out of 28 joints)	4.4 ± 4.6
Swollen joint count (out of 28 joints)	2.7 ± 2.6
CRP (mg/dl)	1.6 ± 2.6
Physician VAS	40.2 ± 22.0
Patient VAS	44.9 ± 25.7
CDAI	15.5 ± 20.6
SDAI	17.1 ± 24.1
MTX Dosage (mg/week)	4.9 ± 4.7
PSL dosage (mg/day)	2.7 ± 3.1
Rheumatoid factor positive rate	72.9
Anti-CCP antibody positive rate (%)	74.1
BIO use history: 1 drug	44
BIO use history: 2 drugs	43
BIO use history: 3 or more drugs	45

treatment and were excluded from the analysis. The baseline characteristics of the patients who were administered optimal doses according to renal function are shown in Table 2. The 2 mg group had a significantly longer disease duration, lower MTX dosage, and lower ACCP antibody positivity rate. After propensity score matching, there were no statistically significant differences in baseline characteristics between the two groups.

Efficacy outcomes

Changes in TJC28, SJC28, EGA, PGA, CRP, and low disease activity and remission rates on the CDAI and SDAI at the start of administration and at 4, 12, 24, and 52 weeks after administration in the matched groups are shown in Fig. 1.

TJC28 improved over the 52 weeks post-treatment in both groups, from 3.7±2.9 at the start of administration to 1.1±0.9 at 52 weeks in the 2 mg group, and from 3.0±3.2 to 1.8±3.5 in the 4 mg group (Fig. 1a). Similarly, SJC28 improved over the 52 weeks post-treatment in both groups, from 2.3±2.6 to 0.5±0.8 in the 2 mg group, and from 2.3±1.9 to 0.7±1.7 in the 4 mg group (Fig. 1b). No statistically significant differences were observed in the TJC28 or SJC28 values between the two groups at any time point.

Global assessment values also improved at 52 weeks post-treatment in both groups. EGA improved from 38.1±19.7 to 11.1±15.3 in the 2 mg group, and from 32.5±22.3 to 14.3±15.3 in the 4 mg group (Fig. 1c). PGA improved from 43.7±26.3 to 12.4±13.0 in the 2 mg group, and from 36.9±27.1 to 20.0±18.4 in the 4 mg group (Fig. 1d). No statistically significant differences were observed in the EGA or PGA values between the two groups at any time point. CRP levels reduced over the 52 weeks post-treatment in both groups, with no statistically significant differences between the two groups at any time point (Fig. 1e).

Low disease activity and remission rates, as measured by the CDAI and SDAI, were not significantly different between the two groups at any time point. The CDAI and SDAI values improved after treatment and peaked at 12 weeks after treatment, following which they plateaued or decreased slightly until 52 weeks after treatment (Fig. 1f, g).

The retention rate during the observation period was 69.7% in the 2 mg group and 75.8% in the 4 mg group, with no significant differences between the two groups ($p=0.54$) (Fig. 2).

Safety outcomes

Adverse events were reported with a higher frequency in the 4 mg dosage group (64.0%) compared to the 2 mg group (39.6%) (Table 3). The most notable AEs were infections and infestations, occurring in 19.8% of the 4 mg group, while only 5.7% experienced this in the 2 mg group. Other significant categories included respiratory

Table 2 Baseline characteristics of patients in 2 mg and 4 mg groups before and after propensity score matching

	Before matching			After matching		
	2 mg	4 mg	*P* value	2 mg	4 mg	*P* value
Number of cases	53	86		33	33	
Age (y)	61.3±12.1	57.4±15.5	0.106	59.2±11.8	59.5±14.6	0.934
Sex	46 women; 7 men	69 women; 17 men	0.306	26 women; 7 men	25 women; 8 men	0.769
Height (cm)	154.2±9.8	153.4±7.8	0.425	153.2±6.7	155.2±4.8	0.798
Weight (kg)	55.7±9.8	56.8±10.2	0.582	55.7±9.4	56.2±9.2	0.824
BMI (kg/m2)	22.9±3.29	23.0±3.40	0.84	23.2±3.19	22.9±2.80	0.756
Disease duration (years) (±SD)	15.4±12.0	9.9±8.5	0.004*	11.6±8.4	11.3±8.2	0.868
Tender joint count (out of 28 joints)	4.2±3.5	5.0±5.5	0.28	3.7±2.9	3.0±3.3	0.365
Swollen joint count (out of 28 joints)	2.8±3.1	2.6±2.4	0.77	2.3±2.7	2.3±2.0	0.958
CRP (mg/dl)	1.8±2.2	1.4±2.5	0.405	1.5±1.6	1.4±2.9	0.938
Physician VAS (±SD)	42.8±21.7	38.5±23.0	0.289	38.1±20.0	32.5±22.6	0.289
Patient VAS (±SD)	46.3±25.7	44.3±26.8	0.669	43.7±26.8	36.9±27.5	0.316
CDAI	15.8±8.0	15.8±9.6	0.98	14.2±7.8	12.3±7.6	0.311
SDAI	17.6±9.3	17.3±10.1	0.853	15.6±8.3	13.7±8.5	0.349
MTX Dosage (mg/week)	3.9±4.0	5.8±5.0	0.017*	4.4±4.3	5.9±4.6	0.163
PSL dosage (mg/day)	2.9±2.8	2.5±3.4	0.44	3.0±2.8	2.4±3.5	0.395
Rheumatoid factor positive rate	74.8	71.9	0.66	73.8	72.2	0.662
Anti-CCP antibody positive rate (%)	50.4	75.6	0.0453*	72.7	78.8	0.566
BIO use history: 1 drug	11	23		6	12	
BIO use history: 2 drugs	10	20		6	9	
BIO use history: 3 or more drugs	17	30		11	5	
eGFR	46.3±12.9	79.1±17.2		43.6±14.2	82.1±20.4	

* $P<0.05$

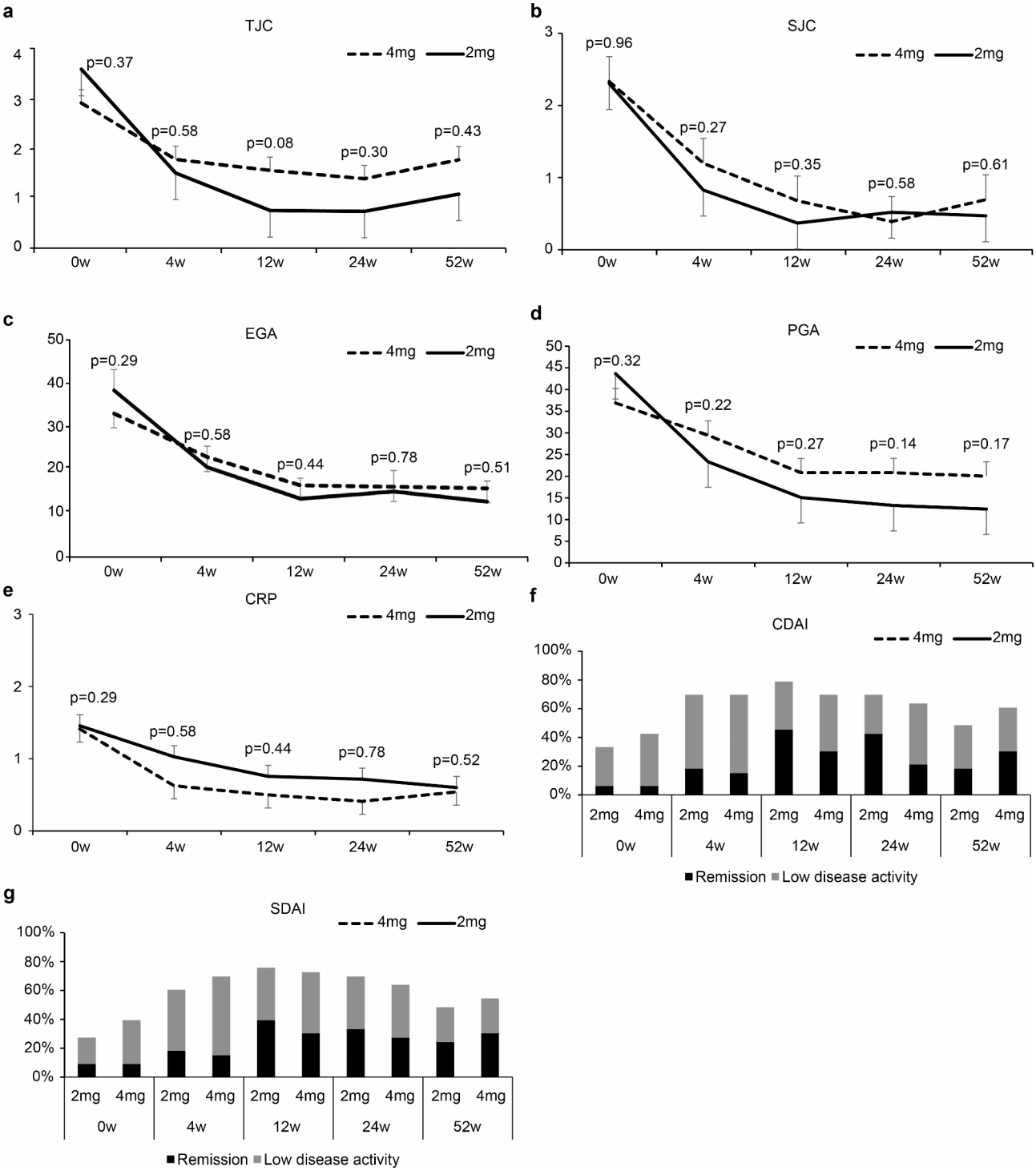

Fig. 1 Outcomes over 52 weeks following treatment in the matched 4 mg and 2 mg groups showing changes in (**a**) TJC28, (**b**) SJC28, (**c**) EGA, (**d**) PGA, (**e**) CRP, and low disease activity and remission rates on the (**f**) CDAI and (**g**) SDAI

disorders (10.5% in the 4 mg group) and liver dysfunction (7.0% in the 4 mg group). Overall, 32.4% of participants experienced AEs, with a higher incidence in the higher dosage group (24.5% in the 2 mg group and 37.2% in the 4 mg group). Other less common AEs included gastrointestinal, skin, and nervous system disorders, with overall cases of AEs totaling 76 across both groups. No cases of venous thromboembolism (VTE) occurred in either group. The adverse event outcomes were mild in all cases except for one instance of sudden death.

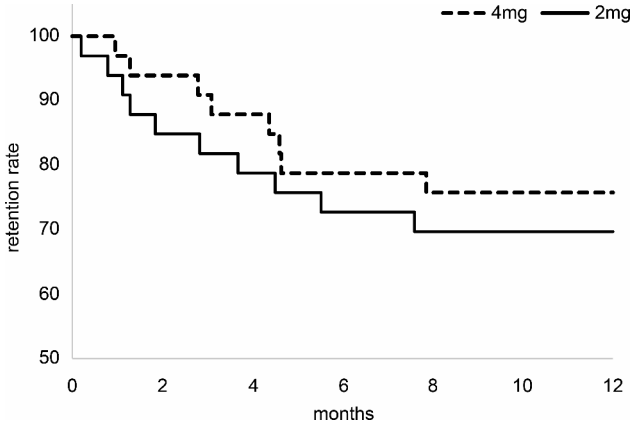

Fig. 2 Retention rates in the 4 mg and 2 mg groups

The drug was discontinued in 11 out of 139 patients (8%) due to adverse events. In the 2 mg group, discontinuation was linked to one case each of fatigue, dizziness, stomatitis, epigastric pain, and nausea, while one case had an unknown cause. In the 4 mg group, discontinuation occurred due to one case of extrapulmonary tuberculosis, one of malaise, and one of *Pneumocystis* pneumonia, with two cases also having an unknown cause.

Discussion

This study provided an important finding: The efficacy and retention rate of 2 mg baricitinib administered to patients with moderate renal impairment is the same as 4 mg baricitinib administered to patients with no impaired renal function. For JAK inhibitors, which are indicated for RA in Japan, the dose must be adjusted according to the severity of liver and renal dysfunction from the perspective of their metabolism and excretion [20,21]. For example, it is recommended that tofacitinib be administered at half doses because the AUC concentration approximately doubles [22]. Similarly, baricitinib 2 mg was administered to patients with moderate renal impairment, whereas baricitinib 4 mg was administered to patients with normal renal function. This is the first study to report the efficacy and retention rate of baricitinib 2 mg in a real-world setting in patients with moderate renal dysfunction in Japan.

Between-group comparisons of the patients' baseline characteristics before propensity score matching showed that the 2 mg group had a significantly longer disease duration, lower MTX dosage, and lower ACCP antibody positivity rate. These results suggest that baricitinib 2 mg may be administered in real-world cases where renal function is decreased, an increase in the MTX dose is difficult, or patients have intractable seronegative RA.

Furthermore, the efficacy of baricitinib did not differ significantly between the two dose groups after adjusting for propensity score matching, demonstrating that baricitinib 2 mg is as effective as baricitinib 4 mg in RA patients with moderate renal dysfunction. The retention rate during the 52-week observation period did not differ between the two dose groups. These results are in agreement with those of an observational study that revealed that the discontinuation rate of baricitinib did not differ between the 2 mg and 4 mg groups in patients followed up for 2 years, suggesting that baricitinib 2 mg is also useful in patients with moderate renal dysfunction [23].

The present results, though limited by the small number of cases, suggest higher incidence rates of adverse events, infections, and herpes zoster in the 4 mg group compared to the 2 mg group. However, the incidences of interstitial pneumonitis, malignant tumors, and VTE remained low and did not exceed previously reported rates [24, 25]. A recent study of all RA patients treated with baricitinib in Japan found no dose-dependent relationship in the incidence of adverse events or serious infections between the 2 mg and 4 mg groups, despite the older age of patients in the 2 mg group [25]. Herpes zoster incidence, however, has been reported as dose-dependent in Japanese RA patients [25], aligning with the observations of this study. Similarly, clinical trials have also shown a dose-dependent trend in general infections during the placebo-controlled 24 week period [26]. Adverse events are expected to decrease with dose reductions as they are linked to Cmax and AUC of drug concentrations in the blood. Given the limited sample size in this analysis, larger studies are required to confirm the dose dependency of adverse events related to baricitinib, particularly in relation to renal function. The data from this study, along with the nearly equal efficacy of the 2 mg and 4 mg doses reported in the RA-BUILD study [16], suggest that the 2 mg dose may offer an optimal benefit-risk profile for the Japanese population – something that the Fukuoka registry could further clarify in future studies.

The FDA has reported that 4 mg of baricitinib is associated with an increased risk of VTE, a notable adverse event [27]. Although the mechanism by which VTE occurs in association with baricitinib is unknown, age and BMI have been reported to be risk factors for VTE when baricitinib is used. VTE was not observed in any patient in this study. This may be explained by the fact that Japanese patients with RA have a low BMI (a risk factor for VTE), although their mean age is higher. The incidence of VTE is reportedly 0.35/100 person-years [25]. In this study, the incidence rate was within this range, although the observation period was short.

This study had several limitations. First, it was retrospective in nature and based on a small sample size, which may have been underpowered to detect differences between the two dosage groups. Second, the follow-up

Table 3 Adverse events in the 2 mg and 4 mg groups

System Organ Class/ Preferred Term	2 mg (*n* = 53)	4 mg (*n* = 86)	Total (*n* = 139)
Infections and infestations	**3 (5.7%)**	**17 (19.8%)**	**20 (14.4%)**
Atypical mycobacteriosis	1 (1.9%)	0 (0.0%)	1 (0.7%)
Bronchitis	0 (0.0%)	1 (1.2%)	1 (0.7%)
Cellulitis of both legs	0 (0.0%)	1 (1.2%)	1 (0.7%)
Conjunctivitis	0 (0.0%)	1 (1.2%)	1 (0.7%)
Cytomegalovirus	0 (0.0%)	1 (1.2%)	1 (0.7%)
Herpes zoster	2 (3.8%)	6 (7.0%)	8 (5.8%)
Periungual abscess	0 (0.0%)	1 (1.2%)	1 (0.7%)
Pharyngitis	0 (0.0%)	1 (1.2%)	1 (0.7%)
Pneumocystis pneumonia	0 (0.0%)	1 (1.2%)	1 (0.7%)
Sinusitis	0 (0.0%)	1 (1.2%)	1 (0.7%)
Suspected cervical tuberculosis	0 (0.0%)	1 (1.2%)	1 (0.7%)
Upper respiratory tract inflammation	0 (0.0%)	1 (1.2%)	1 (0.7%)
Viral infections	0 (0.0%)	1 (1.2%)	1 (0.7%)
General disorders and administration site conditions	**5 (9.4%)**	**4 (4.7%)**	**9 (6.5%)**
Discomfort	2 (3.8%)	0 (0.0%)	2 (1.4%)
Feeling bad	0 (0.0%)	1 (1.2%)	1 (0.7%)
Fever	2 (3.8%)	0 (0.0%)	2 (1.4%)
Foggy head	0 (0.0%)	1 (1.2%)	1 (0.7%)
Malaise	1 (1.9%)	2 (2.3%)	3 (2.2%)
Respiratory, thoracic and mediastinal disorders	**0 (0.0%)**	**9 (10.5%)**	**9 (6.5%)**
Common cold	0 (0.0%)	3 (3.5%)	3 (2.2%)
Influenza	0 (0.0%)	2 (2.3%)	2 (1.4%)
Interstitial pneumonitis	0 (0.0%)	1 (1.2%)	1 (0.7%)
Wheezing	0 (0.0%)	1 (1.2%)	1 (0.7%)
Epistaxis	0 (0.0%)	1 (1.2%)	1 (0.7%)
Old inflammatory nodule of the right middle lobe	0 (0.0%)	1 (1.2%)	1 (0.7%)
Hepatobiliary disorders	**2 (3.8%)**	**6 (7.0%)**	**8 (5.8%)**
Liver dysfunction	1 (1.9%)	6 (7.0%)	7 (5.0%)
Obstructive jaundice	1 (1.9%)	0 (0.0%)	1 (0.7%)
Gastrointestinal disorders	**3 (5.7%)**	**2 (2.3%)**	**5 (3.6%)**
Anorexia	1 (1.9%)	0 (0.0%)	1 (0.7%)
Epigastric pain	0 (0.0%)	1 (1.2%)	1 (0.7%)
Hematemesis	0 (0.0%)	1 (1.2%)	1 (0.7%)
Nausea	1 (1.9%)	0 (0.0%)	1 (0.7%)
Stomach pain	1 (1.9%)	0 (0.0%)	1 (0.7%)
Skin and subcutaneous tissue disorders	**1 (1.9%)**	**3 (3.5%)**	**4 (2.9%)**
Depilation	1 (1.9%)	0 (0.0%)	1 (0.7%)
Discoloration of the left toenail	0 (0.0%)	1 (1.2%)	1 (0.7%)
Rash	0 (0.0%)	1 (1.2%)	1 (0.7%)
Right eyelid herpes	0 (0.0%)	1 (1.2%)	1 (0.7%)
Eye disorders	**1 (1.9%)**	**2 (2.3%)**	**3 (2.2%)**
Blurred vision	0 (0.0%)	1 (1.2%)	1 (0.7%)
Eye dryness	1 (1.9%)	0 (0.0%)	1 (0.7%)
Glaucoma	0 (0.0%)	1 (1.2%)	1 (0.7%)
Nervous system disorders	**1 (1.9%)**	**5 (5.8%)**	**6 (4.3%)**
Numbness	0 (0.0%)	2 (2.3%)	2 (1.4%)
Insomnia	1 (1.9%)	1 (1.2%)	2 (1.4%)
Vertigo	0 (0.0%)	1 (1.2%)	1 (0.7%)
Left-sided body torsion	**0 (0.0%)**	**1 (1.2%)**	**1 (0.7%)**
Renal and urinary disorders	**1 (1.9%)**	**1 (1.2%)**	**2 (1.4%)**
Renal dysfunction	0 (0.0%)	1 (1.2%)	1 (0.7%)
Urinary tract stones	1 (1.9%)	0 (0.0%)	1 (0.7%)

Table 3 (continued)

System Organ Class/ Preferred Term	2 mg (*n* = 53)	4 mg (*n* = 86)	Total (*n* = 139)
Vascular disorders	**0 (0.0%)**	**2 (2.3%)**	**2 (1.4%)**
Elevated blood pressure	0 (0.0%)	1 (1.2%)	1 (0.7%)
Unstable angina	0 (0.0%)	1 (1.2%)	1 (0.7%)
Metabolism and nutrition disorders	**0 (0.0%)**	**2 (2.3%)**	**2 (1.4%)**
Anaemia	0 (0.0%)	1 (1.2%)	1 (0.7%)
Dyslipidemia	0 (0.0%)	1 (1.2%)	1 (0.7%)
Reproductive system and breast disorders	**0 (0.0%)**	**1 (1.2%)**	**1 (0.7%)**
Irregular menstruation	0 (0.0%)	1 (1.2%)	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (3.8%)**	**0 (0.0%)**	**2 (1.4%)**
Pancreatic head carcinoma	1 (1.9%)	0 (0.0%)	1 (0.7%)
Coccygeal tumor	1 (1.9%)	0 (0.0%)	1 (0.7%)
Cardiac disorders	**1 (1.9%)**	**1 (1.2%)**	**2 (1.4%)**
Sudden death	0 (0.0%)	1 (1.2%)	1 (0.7%)
Epicarditis	1 (1.9%)	0 (0.0%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	**1 (1.9%)**	**0 (0.0%)**	**1 (0.7%)**
Bilateral shoulder fractures	1 (1.9%)	0 (0.0%)	1 (0.7%)
Total AEs	**21 (39.6%)**	**55 (64.0%)**	**76 (54.7%)**
# Patients with AEs	**13 (24.5%)**	**32 (37.2%)**	**45 (32.4%)**

period was relatively short; long-term studies are needed to evaluate the safety and efficacy of baricitinib in patients with RA. Third, the dataset contained several missing values that were handled using non-responder imputation. To address the problem of missing data, we applied the Last Observation Carried Forward (LOCF) method, which may increase the risk of errors. Finally, although we used propensity score matching to compare the dosage groups based on their baseline characteristics, the groups may have still differed in terms of other variables that were not measured in the study. The propensity score matching process probably excluded patients with a longer course of disease, low MTX or low ACCP antibody positivity rate, and hence the conclusions derived from the study should be considered with caution. Large-scale prospective interventional studies are necessary to better compare the safety and efficacy of baricitinib in patients with RA and renal dysfunction.

Conclusions

This retrospective multicenter study, based on standardized data collection, indicated that the efficacy and retention rate of baricitinib 2 mg administered to RA patients with moderate renal dysfunction is equivalent to baricitinib 4 mg administered to RA patients without renal dysfunction. In addition, the safety of baricitinib was within the range of previously reported incidences.

Abbreviations

ACPA	Anti-citrullinated protein antibody
ACR	American college of rheumatology
AUC	Area under the curve
b/tsDMARDs	Biologic and targeted synthetic disease-modifying antirheumatic drugs
BMI	Body mass index
CDAI	Clinical disease activity index
CRP	C-reactive protein
DMARDs	Disease-modified antirheumatic drugs
EGA	Evaluator global assessment
eGFR	Estimated glomerular filtration rate
EULAR	European league against rheumatism
FDA	Food and drug administration
JAK	Janus kinase
MTX	Methotrexate
PGA	Patient global assessment
RA	Rheumatoid arthritis
SDAI	Simplified disease activity index
tsDMARDs	Targeted synthetic disease-modifying antirheumatic drugs
VTE	Venous thromboembolism

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Author contributions
MK, HH, ES, RN, TT, YI, MN, and HN enrolled the study patients and contributed the data included in the manuscript. AM drafted the manuscript. MK, HH, ES, RN, TT, YI, MN, YY, HN, YN, and TY reviewed the manuscript and revised it critically on intellectual content. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted with the approval of the Ethics Review Committee (Haradoi Hospital Ethical Review Board: Approval No. 2019006). This study is a multicenter study. In addition, Haradoi Hospital was the institute of the Ethical Review Committee decided by the Kondo Clinic of Rheumatology and Orthopaedic Surgery, the lead institution of the study. All the patients provided informed verbal consent to participate in this study. The procedure of obtaining informed verbal consent was approved by Haradoi Hospital Ethical Review Board.

Consent for publication
Not applicable.

Competing interests
HN has received lecture fees or grants from Asahi Kasei Pharma Corporation, Eisai Co., Ltd., GlaxoSmithKline K.K., Bristol Myers Squibb, Nippon Boehringer Ingelheim Co., Ltd. and Chugai Pharmaceutical Co., Ltd. The other authors have no competing interests to declare.

Author details
[1]Department of Orthopaedic Surgery, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
[2]Kondo Clinic of Rheumatology and Orthopaedic Surgery, 3-10-11 Tenjin, Chuo-ku, Fukuoka 810-0001, Japan
[3]Department of Orthopaedic Surgery Rheumatology Center, Yagi Hospital, 2-21-25, Maidashi, Higashi-ku, Fukuoka 812-0054, Japan
[4]Shono Rheumatology Clinic, Nishijin Prime Building, 1-10-27, Nishijin, Sawara-ku, Fukuoka 814-0002, Japan
[5]Nagamine Rheumatology and Orthopaedic Clinic, 1-11-1, Kashiiekimae, Higashi-ku, Fukuoka 813-0013, Japan
[6]PS Clinic, Random Square, 6-18 Tenya-cho, Hakata-ku, Fukuoka 812-0025, Japan
[7]Department of Rheumatology, Fukuoka Red Cross Hospital, 3-1-1 Ogusu, Minami-ku, Fukuoka 815-8555, Japan
[8]Division of Rheumatology, Kurume University Medical Center, 155-1 Kokubu-machi, Kurume 839-0863, Fukuoka, Japan
[9]Department of Medical Education, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[10]Department of Orthopaedic Surgery, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

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