Real-World Comparative Effectiveness and Safety of Tofacitinib and Baricitinib in Patients with Rheumatoid Arthritis

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Abstract

Objective: To compare the efficacy and safety of tofacitinib and baricitinib in patients with RA in a real-world setting.

Methods: A total of 242 patients with RA who were treated with tofacitinib (n=161) or baricitinib (n=81) were enrolled. To avoid confounding, we performed propensity score matching based on multiple baseline characteristic variables, and then 80 baricitinib-treated patients and 57 tofacitinib-treated patients were extracted for direct comparison. Their clinical disease activity and AEs were evaluated for 24 weeks.

Results: The mean DAS28-ESR change from baseline to 24 weeks were 1.60 (tofacitinib) and 1.46 (baricitinib). There was no significant difference in the clinical response between two groups. The efficacy was not significantly changed in the patients without concomitant MTX use in both groups, but the concomitant MTX use showed better clinical efficacy in the cases of baricitinib treatment. In both groups, the most common AE was herpes zoster infection, and the AE rates were similar between the two groups. However, the predictive factors contributing to clinical response as revealed by a multivariable logistic analysis differed. The concomitant oral steroid use was independently associated with the achievement of DAS-low disease activity in both groups, whereas in the baricitinib group, the number of biological and/or targeted synthetic DMARDs previously used was also associated.

Conclusions: Our findings indicate that tofacitinib and baricitinib had comparable continuing efficacies and safety profiles. However, the influence of clinical characteristics on the treatment response differed. Direct comparison provides useful information to optimal use of JAK inhibitors in real-world settings.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by chronic synovitis that symmetrically develops in joints, and persistent inflammation in joints leads to the destruction of joints and tendons, resulting in deformities and ankylosis. Rheumatoid arthritis affects approx. 0.5–1% of the population worldwide. The use of biological disease-modifying antirheumatic drugs (bDMARDs) — which are able to selectively interfere with a specific molecule such as tumor necrosis factor-alpha (TNF-α) or a cellular pathway such as T-cell activation — enables the achievement of low-disease activity or even remission in a high percentage of cases.\(^1,2\) In addition to bDMARDs, recently, Janus kinase (JAK) inhibitors can be used to treat RA and are beginning to play a crucial role in the management of RA.\(^3\) Because the JAK pathway is involved in many biologic functions (including the activation of the inflammatory cascade in immune cells) and is associated with several cytokines that are closely related to the pathogenesis of RA,\(^4\) blockade of the JAK pathway is effective in RA treatment.

Tofacitinib is a non-selective first-generation JAK inhibitor that acts by inhibiting JAK1, JAK2, JAK3 and to a lesser extent TYK2. Six pivotal randomized phase II clinical studies demonstrated RA patients’ good treatment response to tofacitinib among patients with differing statuses such as methotrexate (MTX)-
naïve subjects, and the studies revealed the patients' inadequate response to MTX/bDMARDs.\textsuperscript{5–10} Moreover, several studies in real-world settings indicated that tofacitinib was as effective as was observed in these phase III trials.\textsuperscript{11,12}

After the approval of tofacitinib in 2012 (U.S.) and 2013 (Japan), baricitinib was approved for the treatment of RA in 2018 (U.S.) and 2017 (Japan). Baricitinib prevents the activation of JAK1 and JAK2. As with tofacitinib, the clinical efficacy of baricitinib was assessed by several randomized phase \textsuperscript{1} clinical studies, and these studies showed the usefulness of baricitinib as a mono- or combo-therapy for patients with RA.\textsuperscript{13–16} Regarding the two drugs' pharmacological action, baricitinib acts more selectively on JAK1 than tofacitinib, and for example baricitinib thus strongly prevent STAT phosphorylation by interleukin (IL)-6\textsuperscript{17}. On the other hand, tofacitinib acts on JAK3, which baricitinib cannot inhibit. Considering such differences, the treatment response might be different even between these two JAK inhibitors. However, until now, no published data of a direct comparison among JAK inhibitors in RA have been available, and the efficacy and safety of these JAK inhibitors, especially baricitinib, in a real-world setting have rarely been described. It is important to determine the differences and similarities of these JAK inhibitors in a real-world setting for the treatment of RA, so that the optimal agent can be administered in each case or population.

Direct comparisons of clinical efficacy among treatments are generally scarce in randomized controlled trials (RCTs), especially in RA treatment. However, by adopting appropriate methods such as propensity score matching to control for bias, the data from observational studies can be used for a direct comparison. We conducted the present study to directly compare the efficacy and safety of tofacitinib with those of baricitinib by using propensity score (PS) matching in a real-world setting. We also analyzed the respective factors that contribute to the clinical response to each of these JAK inhibitors.

**Patients And Method**

**Patients**

All patients were registered in this study at one of the following institutions: the Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Sasebo Chuo Hospital, Isahaya General Hospital, Sasebo City General Hospital, and the Japanese Red Cross Nagasaki Genbaku Hospital. A total of 242 patients who were treated with tofacitinib (n = 161) between August 2013 and October 2019 or baricitinib (n = 81) between January 2018 and February 2020 were enrolled. All patients had a diagnosis of RA based on the 2010 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria for RA.\textsuperscript{18}

We collected the enrolled patients' data at the initiation of each treatment, including the disease duration, positivity of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), history of previous disease-modifying antirheumatic drugs (DMARDs), and concomitant medications. The treatment with tofacitinib or baricitinib was administered by the patients' attending rheumatologists in accord with the
Japan College of Rheumatology (JCR) guidelines. The patients received either 5 mg of tofacitinib twice/once daily (in patients with renal impairment) daily or 4 mg/2 mg (in patients with renal impairment) of baricitinib once daily with no change in any concomitant csDMARD therapy during the 24-week observation period. The patients gave their informed consent to be subjected to the protocol, which was approved by the Institutional Review Board of Nagasaki University (IRB approval no. 11032819).

**Clinical efficacy and safety**

The patients' clinical disease activity was assessed using the Disease Activity Score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) at the baseline and at 4, 8, 12, 16, 20, and 24 weeks after the initiation of tofacitinib or baricitinib treatment. Safety was also assessed based on the adverse events (AEs) reported by the patients as well as on the findings of physical examinations until 24 weeks.

**Propensity score matching**

To compare efficacy and safety in this study, we attempted to control confounding using PS matching\textsuperscript{19}. The covariates included in the logistic regression model for estimating PS were selected from subject-matter knowledge and a directed acyclic graph. Selected covariates were sex, age, disease duration, methotrexate (MTX) use, oral steroid use, the number of previous biological/target synthetic DMARDs use, DAS28-ESR, SDAI, presence of RF, and anti-citrullinated protein antibodies ACPA. The PS matching was performed at the nearest neighbor matching with the caliper set to 0.2 using MatchIt package in R\textsuperscript{20}. The validity of the PS matching was confirmed by standardized differences and plot using cobalt package in R\textsuperscript{21}.

**Statistical analysis**

Before and after the PS matching, we summarized and compared the baseline demographic and disease characteristics between the baricitinib-treated and tofacitinib-treated patients. The continuous variables were compared by Wilcoxon's rank sum test and are presented as the medians with interquartile range (IQR). The categorical variables were compared by Fisher's exact test and are presented as the number of patients and percentages.

For the evaluation of efficacy, first, we conducted a mixed effect model with a repeated measures analysis of variance (ANOVA) to ascertain whether there were significant differences in clinical efficacy between the two treatment groups during the treatment period, using the PS matching data. The model included the treatment group, treatment period, baseline efficacy, and the multiple term of group and period. Second, to estimate the disease activity at week 24, we used the last observation carried forward (LOCF) method for patients who withdrew before week 24 and in cases of missing data. Fisher's exact tests were used to compare the groups. Third, we summarized the disease activity between groups with and without MTX treatment by percentage and compared the values with Fisher's exact test.
For the evaluation of safety and drug retention rate, we first summarized and compared the adverse events before and after the PS matching. We then estimated the drug retention rate in each group by the Kaplan-Meier method and compared them by the log-rank test.

Finally, we evaluated the predictive factor of clinical responses by performing univariate and multivariable logistic regression analyses. Variables with p-values < 0.15 in the univariate logistic regression analyses were entered in the multivariate logistic regression analysis. The statistical significance for all tests was defined by a two-tailed p-value < 0.05. Analyses were performed using R ver. 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), GraphPad prism software (GraphPad Software, San Diego, CA), and JMP Statistical Software (SAS Institute, Cary, NC).

Results

Baseline characteristics

The patients' baseline demographic and disease characteristics are summarized in Table 1. In the unmatched full sample cohort, the tofacitinib-treated patients had worse disease activity scores, longer disease durations, more concomitant use of MTX, and lower RF positivity compared to the baricitinib-treated patients. To avoid confounding, we used PS to match the two groups' baseline characteristics and make them comparable. After the PS matching based on the aforementioned critical characteristics, 57 of the 161 tofacitinib-treated patients and 80 of the 81 baricitinib-treated patients were extracted. With this PS matching, the critical characteristics were well balanced between the two groups.
|                                | **Unmatched cohort** | **Matched cohort** |     |
|--------------------------------|----------------------|-------------------|-----|
|                                | Tofacitinib (n = 161) | Baricitinib (n = 81) | **P value** |
| Female, n (%)                  | 133 (82.6)           | 68 (84.0)         | 0.857 |
| Age (years)                    | 67 [58–73]           | 66 [56–74]        | 0.667 |
| Duration of RA (year)          | 12 [6–18]            | 11 [4–18]         | 0.243 |
| Concomitant MTX use, n (%)     | 109 (67.7)           | 37 (45.7)         | 0.001 |
| Mean MTX dose (mg/week)        | 8.62 ± 2.49          | 8.05 ± 2.69       | 0.427 |
| Concomitant oral steroid use, n (%) | 86 (53.4)       | 38 (46.9)         | 0.345 |
| Mean oral steroid dose (mg/day) | 4.80 ± 2.72         | 4.80 ± 3.08       | 0.844 |
| ACPA positive, n (%)           | 124 (77.0)           | 65 (80.2)         | 0.624 |
| RF positive, n (%)             | 122 (75.8)           | 70 (86.4)         | 0.064 |
| No prior use of b/tsDMARDs, n (%) | 37 (23.0)        | 18 (22.2)         | > 0.999 |
| Number of previous use of b/tsDMARDs | 2.00 [1.00–3.00] | 2.00 [1.00–3.00] | 0.968 |
| DAS28-ESR                      | 5.17 [4.08–6.11]     | 5.13 [4.21–5.98]  | 0.622 |
| SDAI                           | 20 [14–32]           | 19 [14–29]        | 0.507 |
| CDAI                           | 19 [12–30]           | 18 [12–27]        | 0.497 |

Data are median [interquartile range] unless otherwise indicated.

RA rheumatoid arthritis, MTX methotrexate, ACPA anti-citrullinated protein antibodies, RF rheumatoid factor, b/tsDMARDs biological and/or targeted synthetic disease-modifying antirheumatic drugs, DAS disease activity score, ESR erythrocyte sedimentation rate, SDAI simplified disease activity index, CDAI clinical disease activity index
In the matched cohort, the patients treated with tofacitinib exhibited high-moderate disease activity (DAS28-ESR: 5.20, SDAI: 19, CDAI: 18) with the median age of 68 years and median disease duration of 11 years. The patients treated with baricitinib also exhibited high-moderate disease activity (DAS28-ESR: 5.17, SDAI: 19, CDAI: 18) with the median age of 66 years and median disease duration of 11 years. The concomitant use of MTX at baseline was present in 63% of the tofacitinib group and 46% of the baricitinib group. A concomitant use of an oral steroid was present in 46% of the tofacitinib group and 48% of the baricitinib group. Approximately 80% of the patients in both groups had been treated with a biological or/and targeted synthetic (b/ts) DMARD (the median number of previous uses of b/tsDMARDs was 2 in both groups). Regarding switching from another JAK inhibitor, none of the patients in the tofacitinib group had been treated with another JAK inhibitor, whereas 26 of the patients in the baricitinib group had been treated with tofacitinib.

**Clinical efficacy**

Figure 1 illustrated the changes in the DAS28-ESR values of the matched cohort over the 24-week study period. The mean DAS28-ESR score for the tofacitinib-treated patients decreased significantly from 4.92 at baseline to 3.32 at 24 weeks. The baricitinib-treated patients also showed a significantly improved DAS28-ESR from 5.03 at baseline to 3.57 at 24 weeks. At the 24-week follow-up, the DAS28-ESR, SDAI, and CDAI remission rate were 21.1%, 24.6% and 17.5% in the tofacitinib group and 25.0%, 27.5% and 22.5% in the baricitinib group, respectively. The rate of patients who achieved less than low disease activity of each clinical indicators (DAS28-ESR, SDAI, CDAI) were 36.8%, 68.4%, 71.9% in tofacitinib-treated group and 45.0%, 61.3%, 60.0% in baricitinib-treated group (Table 2). There was no significant difference in the clinical responses of the baricitinib-treated patients and the tofacitinib-treated patients. These results suggest that the efficacy of tofacitinib for RA over a 24-week period and that of baricitinib were similar in daily clinical practice.
Table 2
Disease activity at 24 weeks

|                  | Tofacitinib (n = 57) | Baricitinib (n = 80) | P value |
|------------------|----------------------|----------------------|---------|
| **DAS28-ESR**    |                      |                      |         |
| Remission, n (%) | 12 (21.1)            | 20 (25.0)            | 0.684   |
| LDA achievement, n (%) | 21 (36.8)   | 36 (45.0)            | 0.382   |
| **SDAI**         |                      |                      |         |
| Remission, n (%) | 14 (24.6)            | 22 (27.5)            | 0.844   |
| LDA achievement, n (%) | 39 (68.4)   | 49 (61.3)            | 0.470   |
| **CDAI**         |                      |                      |         |
| Remission, n (%) | 10 (17.5)            | 18 (22.5)            | 0.525   |
| LDA achievement, n (%) | 41 (71.9)   | 48 (60.0)            | 0.203   |

*DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *LDA* low disease activity, *SDAI* simplified disease activity index, *CDAI* clinical disease activity index

We next analyzed the efficacy of each of the JAK inhibitors in subgroups divided by the patients' concomitant use/non-use of MTX. Except for age in baricitinib group, the baseline variables of the subgroups were almost equal regardless of MTX use/non-use (Suppl. Table S1). In the tofacitinib group, the mean DAS28-ESR change from baseline to 24 weeks was 1.40 in the patients with concomitant use of MTX and 1.05 in those without a concomitant use of MTX, whereas in the baricitinib group, the corresponding values were 1.47 and 0.91, respectively.

The proportions of disease activity at 24 weeks defined by the DAS28-ESR are shown in Fig. 2. There were no significant differences in the above indices between the patients with and without concomitant use of MTX in both groups. The good treatment response in the patients without a concomitant use of MTX was also observed in the unmatched cohort (Suppl. Table S2).

**Drug retention and adverse events**

There was no significant difference in the drug retention rate between the tofacitinib and baricitinib groups (log-rank p-value = 0.8). The corresponding Kaplan-Meier plots of discontinuation are illustrated in Fig. 3. During the 24-week follow-up period, 12 patients (21%) were discontinued tofacitinib treatment and 14 patients (18%) were discontinued baricitinib treatment. The reasons for discontinuation were as follows. In the tofacitinib group, lack of efficacy (n = 5) and an AE (pneumonia, herpes zoster, lung cancer, nausea [n = 2], vertigo, and hair loss) (n = 7) were the reasons. In the baricitinib group, lack of efficacy (n = 10) and an AE (pneumonia, herpes zoster, headache, and elevation of creatine kinase) (n = 4) were the reasons.
Table 3 summarizes the AEs experienced by the 12 patients in the tofacitinib group and the 13 patients in the baricitinib group. The incidence rate of AEs was not significantly different between the groups. The most common AE was infection (12.3% in the tofacitinib group, 13.8% in the baricitinib group). Among the infections, as expected, herpes zoster infection was most frequent in both groups (8.8% in the tofacitinib group, 5.0% in the baricitinib group). Only one neoplasm was seen in the matched cohort (lung cancer in tofacitinib-treated patients) during 24 weeks. Although the rate of herpes zoster was higher in the tofacitinib group, the difference was not significant. Moreover, the rates of other AEs such as infection and gastrointestinal disorder were also similar in each subgroup of the treatment groups. The rates of each AE were also not significantly different between the tofacitinib- and baricitinib-treated patients in the unmatched cohort.
|                          | Unmatched cohort | Matched cohort | P value | Unmatched cohort | Matched cohort | P value |
|--------------------------|------------------|----------------|---------|------------------|----------------|---------|
|                          | Tofacitinib (n = 161) | Baricitinib (n = 81) |         | Tofacitinib (n = 57) | Baricitinib (n = 80) |         |
| All Events               | 32 (19.9)        | 17 (21.0)      | 0.866   | 12 (21.1)        | 16 (20.0)      | > 0.999 |
| Infection                | 20 (12.4)        | 11 (13.6)      | 0.840   | 7 (12.3)         | 11 (13.8)      | > 0.999 |
| Herpes zoster, n (%)     | 9 (5.6)          | 4 (4.9)        |         | 5 (8.8)          | 4 (5.0)        |         |
| Pneumonia                | 6 (3.7)          | 1 (1.2)        |         | 1 (1.8)          | 1 (1.3)        |         |
| Upper respiratory infection | 4 (2.5)    | 3 (3.7)        |         | 1 (1.8)          | 3 (3.8)        |         |
| Callus infection         | 1 (1.2)          |               |         | 1 (1.3)          |               |         |
| Cytomegalovirus infection | 1 (1.2)       |               |         | 1 (1.3)          |               |         |
| Fungus infection         | 1 (0.6)          |               |         |                 |               |         |
| Sepsis                   | 1 (1.2)          |               |         | 1 (1.3)          |               |         |
| Gastrointestinal disorder | 6 (3.7)       | 2 (2.5)        | 0.720   | 2 (3.5)          | 2 (2.5)        | > 0.999 |
| Gastric ulcer            | 1 (1.2)          |               |         | 1 (1.3)          |               |         |
| Nausea                   | 4 (2.5)          | 1 (1.2)        |         | 2 (3.5)          | 1 (1.3)        |         |
| Diarrhea                 | 2 (1.2)          |               |         |                 |               |         |
| Neoplasm                 | 3 (1.9)          | 1 (1.2)        | > 0.999 | 1 (1.8)          | 0            | 0.416   |
| Breast cancer            | 1 (1.2)          |               |         |                 |               |         |
| Colon cancer             | 1 (0.6)          |               |         |                 |               |         |
| Skin cancer              | 1 (0.6)          |               |         |                 |               |         |
| Lung cancer              | 1 (0.6)          |               |         | 1 (1.8)          |               |         |
| Others                   | 3 (1.9)          | 3 (3.7)        | 0.405   | 2 (3.5)          | 3 (3.8)        | > 0.999 |
| Hair loss                | 1 (0.6)          |               |         | 1 (1.8)          |               |         |
| vertigo                  | 1 (0.6)          | 1 (1.2)        |         | 1 (1.8)          | 1 (1.3)        |         |
| headache                 | 1 (1.2)          |               |         | 1 (1.3)          |               |         |
We next investigated the factors that contribute to the clinical responses to baricitinib and tofacitinib. The baseline characteristics that predict the achievement of DAS28-ESR-low disease activity (LDA) in the univariate analysis were as follows (Table 4): in the tofacitinib group, the concomitant use of oral steroid and ACPA positivity; in the baricitinib group, concomitant use of an oral steroid, the number of b/tsDMARDs previously used, the DAS28-ESR at the time of treatment initiation, and concomitant use of MTX. Among these factors, the results of the multivariable logistic analysis demonstrated that the concomitant use of an oral steroid was independently associated with the achievement of DAS-LDA in both the tofacitinib and baricitinib groups. Additionally to the concomitant use of an oral steroid, in the baricitinib group, the multivariable analysis also identified the significant association between the association of DAS28-ESR-LDA achievement and the number of b/tsDMARDs previously used, and the DAS-ESR at the time of treatment initiation.

### Table 4: Unmatched cohort vs Matched cohort

|                          | Unmatched cohort | Matched cohort |
|--------------------------|------------------|----------------|
| Interstitial pneumonia   | 1 (0.6)          |                |
| Elevation of creatine kinase | 1 (1.2)      | 1 (1.3)        |

**Comparison of factors contributing to a good clinical response between tofacitinib and baricitinib treatment**
Table 4
Independent predictors for the achievement of LDA at 24 weeks in multivariable analysis

| Variables                      | Tofacitinib |                                      | Baricitinib |                                      |
|-------------------------------|-------------|---------------------------------------|-------------|---------------------------------------|
|                               | Univariate model | Multivariable model | Univariate model | Multivariable model |
|                               | OR (95% CI) | P value                  | OR (95% CI) | P value                  | OR (95% CI) | P value |
| Age (per 1-year increase)     | 1.024       | 0.320                    | 0.985       | 0.425                    |
|                               | (0.976–1.075) |                        | (0.950–1.022) |                        |
| Disease duration (per 1-year increase) | 0.258 | 0.294                    | 0.968       | 0.197                    |
|                               | (0.906–1.032) |                        | (0.921–1.018) |                        |
| Concomitant MTX use (yes/no)  | 1.272       | 0.674                    | 1.99        | 0.130                    |
|                               | (0.412–3.932) |                        | (0.811–4.857) |                        |
| Concomitant oral steroid use (yes/no) | 0.320 | *0.046                 | 0.430       | 0.064                    |
|                               | (0.101–1.013) |                        | (0.174–1.062) |                        |
|                               |            | *0.042                 | 0.289       | *0.028                    |
|                               |            | (0.094–0.992) |                        | (0.092–0.913) |
| Number of previous use of b/tsDMARDs (per drug) | 0.835 | 0.304                    | 0.697       | *0.007                    |
|                               | (0.586–1.190) |                        | (0.529–0.919) |                        |
|                               |            | *0.014                 | 0.674       | *0.014                    |
|                               |            | (0.482–0.943) |                        |                        |
| Inadequate response of another JAK inhibitor (yes/no) | 0.529 | 0.192                    | 0.529       | 0.192                    |
|                               | (0.201–1.394) |                        | (0.201–1.394) |                        |
| DAS28-ESR at baseline (per 1 increase) | 0.779 | 0.213                    | 0.403       | *<0.001                    |
|                               | (0.522–1.162) |                        | (0.252–0.646) |                        |
| ACPA positive (yes/no)        | 3.167       | 0.136                    | 3.422       | 0.123                    |
|                               | (0.614–16.337) |                        | (0.633–18.496) |                        |
|                               |            | 0.196                    | 0.474       | 0.196                    |
|                               |            | (0.151–1.488) |                        |                        |

OR odds raio, 95% CI 95% confidence interval, MTX methotrexate, b/tsDMARDs biological and/or targeted synthetic disease-modifying antirheumatic drugs, JAK janus kinase, DAS disease activity score, ESR erythrocyte sedimentation rate, ACPA anti-citrullinated protein antibodies, RF rheumatoid factor *P < 0.05
|                | Tofacitinib | Baricitinib |
|----------------|-------------|-------------|
| RF positive    | 1.53        | 0.414       |
| (yes/no)       | (0.270–8.699) | (0.111–1.548) |

*OR* odds ratio, 95% CI 95% confidence interval, *MTX* methotrexate, *b/tsDMARDs* biological and/or targeted synthetic disease-modifying antirheumatic drugs, *JAK* janus kinase, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *ACPA* anti-citrullinated protein antibodies, *RF* rheumatoid factor *P* < 0.05

**Discussion**

If superiority or inferiority exists among tsDMARDs, it is very important to determine this information for the algorithm of RA treatment. Knowledge of the baseline variables that influence the treatment response to each tsDMARD is also useful information when selecting a tsDMARD toward the goal of achieving better clinical outcomes, because in RA, many factors affect the treatment responses. For example, patients with shorter disease durations have shown better clinical outcomes with biological DMARDs compared to those with longer disease durations, and the serological status concerning autoimmune antibodies (RF and ACPA) is not only a prognostic factor but also an factor in treatment responses. Unfortunately, no head-to-head RCTs testing JAK inhibitors are available. In the present study, we compared the effectiveness and safety of two JAK inhibitors used to treat RA by using propensity score matching. The findings obtained with our follow-up cohort in real medical practice demonstrated that tofacitinib and baricitinib had comparable efficacies and similar safety profiles but differences in the predictive factors that contribute to their treatment responses.

To avoid the confounding that can arise from these clinical variables, we performed propensity score matching, and by thus reducing the risk of confounding, our direct comparison using propensity scores can be considered reliable even compared with RCTs.

Our analyses revealed that 36.8% of the tofacitinib-treated group and 45.0% of the baricitinib-treated group achieved low disease activity as defined by the DAS28-ESR at 24 weeks, with no significant between-group difference. This result indicated that the two JAK inhibitors are effective and comparable in the daily clinical practice of treating RA patients who have various characteristics and treatment histories. Such a variety of clinical characteristics is different from the cohorts in most RCTs and thus has not been elucidated in RCTs.

It is crucial in RA treatment to know whether the efficacy of a drug depends on the concomitant use of MTX or not. In the present population, the tofacitinib and baricitinib treatments were effective even in patients without a concomitant use of MTX. In those patients, the rates of LDA achievement were 33.3% in the tofacitinib group and 37.2% in the baricitinib group. These results are consistent with those of two phase III trials in which tofacitinib monotherapy and baricitinib monotherapy provided good clinical
Moreover, based on those results, the 2019 EULAR recommendation for the management of RA stated that in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared to other bDMARDs.\textsuperscript{3}

However, in our present investigation, although the difference was not significant the patients with a concomitant use of MTX showed better clinical efficacy compared to those without a concomitant use of MTX in both the tofacitinib and baricitinib groups. The $\Delta$($\Delta$DAS28-ESR from at baseline to at 24 weeks) values from the concomitant use of MTX to without a concomitant use of MTX were 0.35 in the tofacitinib group and 0.56 in the baricitinib group. Considering this result and also a larger study that showed the same tendency,\textsuperscript{25} we suggest that a concomitant use of MTX should be implemented, if possible. Our results also suggested that baricitinib treatment has more advantages in MTX-comedication therapy for the reduction of the DAS28-ESR score compared to tofacitinib treatment. The efficacy of concomitant therapy with MTX might be different for each JAK inhibitor. This point should be verified in studies with larger numbers of patients.

There was no significant difference in the retention rate between the present baricitinib and tofacitinib groups, as ~ about 80\% of the patients continued treatment in both groups. These retention rates are comparable to those of the bDMRADS for which data were acquired from daily clinical practice.\textsuperscript{26–28} In the present study, most of the instances of treatment discontinuation occurred before 12 weeks, and lack of efficacy was the most common discontinuation reason in both groups. This might reflect a treat-to-target strategy even in JAK inhibitor treatment, namely, "until the desired treatment target is reached, drug therapy should be adjusted at least every three months."\textsuperscript{29}

Adverse events occurred in 21.1\% of the tofacitinib group and 20.0\% of the baricitinib group in this study. As with other RCTs, herpes zoster infections were the most frequent AE (8.8 \% in the tofacitinib group and 5.0\% in the baricitinib group). The incidence of herpes zoster infection was higher in the tofacitinib group, and this tendency has also been observed in RCTs. In an integrated analysis of RCTs and long-term extension studies, the incidence per 100 patient-years of herpes zoster was 4.0 in tofacitinib treatment and 3.3 in baricitinib treatment.\textsuperscript{30,31} Although the between-group difference in the herpes zoster infections in our study was not significant and the results of the integrated analysis cannot be compared directly because the patient backgrounds differ, we speculate that this difference might arise from the different selectivity for inhibition of the JAK pathway. Larger and longer-term studies are needed to examine this topic.

Interestingly, we observed that the predictors of treatment response differed by the type of JAK inhibitor. The concomitant use of an oral steroid was associated with the achievement of DAS-LDA in both the baricitinib and tofacitinib groups, whereas the number of b/tsDMARDs previously used was a significant factor only in the baricitinib group. This result is consistent with another study in a real-world setting. Guideli et al. reported that the drug survival of baricitinib is higher in bDMARD-naïve patients.\textsuperscript{32} Considering these results, the initiation of baricitinib at an earlier phase of RA might be better. To
determine the optimal use of different JAK inhibitors in daily clinical practice, further analyses of predictors in real-world settings are necessary.

Limitations of this study are its small sample size and short observation period. Nevertheless, the direct comparison of JAK inhibitors using propensity score matching revealed the non-inferiority of treatment response and safety between the two JAK inhibitors, and it demonstrated a difference in predictors in daily clinical practice. Other potential study limitations should also be taken into account; given that an observational study is prone to different types of confounding, we used propensity matching, but some residual and unmeasured confounding cannot be avoided. In addition, we did not examine the effects on patient-reported outcomes (PROs) such as with a Health Assessment Questionnaire (HAQ) or the 36-item Short Form Health Survey (SF-36). The importance of PROs in RA management has been highlighted in order to reflect the patients' satisfaction with their treatment and their role in making treatment decisions. Furthermore, the administration route of JAK inhibitors is oral, not a subcutaneous/intravenous injection. And, based on their regulation of multiple cytokines, JAK inhibitors have been thought to reduce pain in particular among the symptoms of RA. The patients who are treated with JAK inhibitors might thus be satisfied with their treatments. We will analyze PROs in a future study.

In conclusion, our findings demonstrated that tofacitinib and baricitinib had comparable continuing efficacies and safety profiles. The efficacy of the two drugs was almost the same even without the concomitant use of MTX, but especially in the baricitinib group, the concomitant use of MTX provided better efficacy. A lesser use of previous b/tsDMARDs contributed to the clinical response to baricitinib but not to tofacitinib. Direct comparisons using propensity score matching can provide important and useful information about the optimal use of JAK inhibitors in the management of RA in real-world settings.

**Abbreviations**

RA: rheumatoid arthritis, bDMARDs: biological disease-modifying antirheumatic drugs, JAK: janus kinase, RCTs: randomized controlled trials, PS: propensity score, ACR: American College of Rheumatology, EULAR: European League against Rheumatism, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibodies, JCR: Japan College of Rheumatology, DAS: disease activity score, ESR: erythrocyte sedimentation rate, SDAI: simplified disease activity index, CDAI: clinical disease activity index, AEs: Adverse events, MTX: methotrexate, IQR: interquartile range, LOCF: last observation carried forward, b/ts: biological or and targeted synthetic, PROs: patient-reported outcomes, HAQ: health assessment questionnaire, SF-36: 36-item Short Form Health Survey

**Declarations**

**Ethical Approval and Consent to participate:**

This study was performed in accordance with the Declaration of Helsinki and was approved by the Investigation and Ethics Committee at Nagasaki University. Patients gave their informed consent to be
subjected to the protocol.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that there are no conflicts of interest.

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Authors' contributions:

NI: Conception and design of the study, analysis and interpretation of data and drafting the article. NI, SS: Interpretation of data and perform statistical analysis. NI, TS, AO, KF, TA, AM, YU: Collection and assembly of data. SS, KS, TM, MO, YT, YE, ToS, RS, TK, SK, TI, TA, KI, MT, HN, TO, KE, AK: Analysis and interpretation of data, critical revision the manuscript. YU, AK: supervised the project. All authors have given their final approval of the manuscript to be published as presented.

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