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Nocturnal baricitinib administration leads to rapid drug responses in rheumatoid arthritis: a multicenter non-randomized controlled study

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Abstract

Background Inflammatory cytokine levels exhibit a circadian rhythm in sera, peaking from late night to early morning in patients with rheumatoid arthritis (RA). This cytokine kinetics is a recognized therapeutic target. This clinical study aimed to evaluate the effectiveness of night-time baricitinib administration based on cytokine secretion.

Methods In this 52-week multicenter non-randomized controlled study, 122 patients with RA were assigned to four groups: baricitinib 2 mg morning (BAR2MORN), 2 mg evening (BAR2EVE), 4 mg morning (BAR4MORN), or 4 mg evening (BAR4EVE). The primary endpoint was assessed using the 20% improvement in the American College of Rheumatology criteria (ACR20) at week 12. The secondary endpoints were ACR20/50/70 and changes in the clinical disease activity index (CDAI) through 52 weeks. The results were evaluated using the propensity score inverse probability of treatment weighted to reduce selection bias in patient background.

Results BAR4EVE resulted in better primary endpoint improvement than BAR4MORN (78.2 vs. 43.3%; $p < 0.001$). No difference in improvement was observed in the primary endpoint between BAR2EVE and BAR2MORN (75.5 vs. 60.6%; $p = 0.10$). However, BAR2EVE demonstrated higher ACR20 at weeks 4, 24, and 52 and ACR50 at weeks 4 and 12 than BAR2MORN. BAR4EVE demonstrated higher ACR20/50 at weeks 4, 8, and 12 and ACR70 at weeks 8, 12, and 24 than BAR4MORN. CDAI changes were significantly reduced in BAR4EVE than in BAR4MORN at weeks 4 and 8.

Conclusion Chronotherapy targeting cytokine secretion resulted in rapid drug response, proposing a new potential application for JAK inhibitors.

Trial registration UMIN000040094, July 1, 2020.

Keywords Rheumatoid arthritis, Baricitinib, JAK inhibitor, Chronotherapy

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Background

Rheumatoid arthritis (RA) is a systemic inflammatory arthritis caused by various autoimmune responses with cytokines involved in disease onset, progression, and prognosis [1, 2]. Specifically, Interleukin (IL)-6 and tumor necrosis factor (TNF)-α play key roles in RA pathogenesis. Therefore, biological disease-modifying antirheumatic drugs (bDMARDs) and Janus kinase inhibitors (JAK-I), targeting either IL-6 or TNF-α, help stabilize the disease and set RA treatment goals [3]. However, these treatments are expensive and sometimes ineffective.

The human circadian rhythm, synchronized with the rotation of the Earth, maintaining a 24-h cycle, orchestrates basic life phenomena, including sleep, food intake, energy metabolism, endocrinology, and immune function [4–6]. Moreover, cytokines have a circadian rhythm in patients with RA with inflammatory cytokine secretion, including IL-6 and TNF-α peaking from late night to early morning [7]. Cytokine kinetics in patients with RA is a recognized therapeutic target, with reports on the efficacy of nighttime glucocorticoid (GC) administration dating back to 1964 [8–10]. Specifically, the first successful report on chronotherapy for RA was a double-blind, randomized controlled trial (RCT) demonstrating the efficacy of an extended-release prednisone formulation (MR prednisone) on "morning joint stiffness." MR prednisone administration at night has been reported to significantly improve morning symptoms in patients with RA [11].

As JAK-I half-life is much shorter than that of bDMARDs, the effects of different dosing times on their therapeutic potential can be assessed. Furthermore, we have previously reported that JAK-I baricitinib (BAR) is effective in vivo when administered alongside cytokine secretion [12]. Circadian rhythms have been reported in both collagen-induced arthritis (CIA) mice and patients with RA, with inflammatory cytokines upregulation during sleep [13, 14]. Therefore, we have previously demonstrated significant improvement in arthritis and joint destruction blockage in CIA mice administered BAR during sleep [12].

Improving drug efficacy at the same dose based on "administration time" could substantially impact clinical practice. BAR has been approved for RA treatment at 2 mg by the Food and Drug Administration and at both 2 and 4 mg by the European Medical Agency. Both doses are approved in Japan, with the 2 mg dose recommended for patients aged ≥ 65 years and those with renal dysfunction [15].

Therefore, this trial aimed to assess BAR chronotherapy, based on midnight cytokine secretion, at 2 and 4 mg doses in patients with RA.

Methods

Study design and participants

This 52-week, multicenter, nonrandomized, prospective, open-label trial was conducted at four regional hospitals between May 2020 and August 2024. Patients were assigned to one of four groups: BAR 2 mg morning (BAR2MORN), BAR 2 mg evening (BAR2EVE), BAR 4 mg morning (BAR4MORN), or BAR 4 mg evening (BAR4EVE). The attending physician explained the clinical study to all the patients, and written informed consent was obtained before group allocation. The inclusion criteria were (1) fulfillment of the 2010 American College of Rheumatology (ACR) /European League Against Rheumatism classification criteria for RA [16], (2) age ≥ 18 years, (3) use of conventional synthetic DMARDs for > 3 months (stable dose for ≥ 4 weeks), and (4) not reaching Clinical Disease Activity Index (CDAI) remission. Prior bDMARD and JAK-I use was permitted. Exclusion criteria were (1) severe infection complications, (2) neutropenia (< 500 cells/μL), (3) lymphopenia (< 500 cells/μL), (4) pregnancy, and (5) malignant tumor complications.

Interventions

Based on age, renal function, and economic reasons, a 2 or 4 mg BAR dose was selected in consultation between the patient and the attending physician in a real-world setting. In Japan, 2 mg is recommended for use in patients with moderate renal dysfunction. In daily medical practice, many patients prefer 2 mg owing to the high drug burden, reflecting the diverse backgrounds of the patients taking it. The patients were then alternately assigned to the morning and evening groups. Morning doses were administered between 7 and 10 am, and evening doses were administered between 7 and 10 pm. BAR was prescribed in an outpatient setting per routine medical practice. Until week 12, the concomitant medications were neither increased nor decreased, except in cases of adverse events. If disease activity remained uncontrolled with 2 mg BAR, patients were excluded from the study, and their dosage was increased to 4 mg BAR or switched to another bDMARD or JAK-I. Patients continuing on BAR were followed up for up to 52 weeks.

Outcome measures

The primary outcome was the treatment response in each group, with a 20% improvement in the American College of Rheumatology criteria (ACR20) [17] at week 12. The secondary outcome was the ACR20 response rate at weeks 4, 8, 24, and 52, with 50% (ACR50) and 70% (ACR70) improvement in the ACR criteria at weeks 4, 8, 12, 24, and 52. We also evaluated changes from baseline in ACR components (swollen joint count, SJC; tender joint count, TJC; patient global assessment, PtGA; patient pain; physician global assessment, PGA; Health

Assessment Questionnaire-disability Index, HAQ-DI; erythrocyte sedimentation rate, ESR; and C-reactive protein, CRP); CDAI and Disease Activity Score 28-ESR (DAS28-ESR) at weeks 4, 8, 12, 24, and 52; CDAI and DAS28-ESR remission rates at weeks 12, 24, and 52 [18]; and changes in concomitant GC and methotrexate (MTX) dosage at weeks 24 and 52. Safety was assessed up to week 52 through treatment-emergent adverse events (TAEAs) and laboratory abnormalities. All data were collected in an unblinded manner by a rheumatologist certified by the Japan College of Rheumatology during outpatient visits.

Statistical analysis

Statistical analyses were conducted in patients meeting the inclusion criteria who received at least one BAR dose. Patient characteristics are presented as the median (interquartile range [IQR]), mean ± standard deviation (SD), or number of patients (n). Differences between continuous variables for normally and non-normally distributed groups were analyzed using the two-sided Student's *t*-test and using Mann-Whitney U test, respectively. Categorical variables were compared using Fisher's exact test.

For binary endpoints, ACR20/50/70 response rate, DAS28-ESR, and CDAI remission rate between BAR2MORN versus BAR2EVE or BAR4MORN versus BAR4EVE were analyzed using Pearson's chi-square test after adjusting for propensity score (PS) inverse probability of treatment weighted (IPTW) [19]. To calculate the PS, multivariate logistic regression analysis was used, with BAR2EVE or BAR4EVE as the dependent variable and sex, age, disease duration, concomitant MTX dose, concomitant GC dose, RF positivity, ACPA positivity, number of previous bDMARDs/JAK-I, SJC, TJC, PtGA, CRP, and HAQ-DI as independent variables. Subsequently, weights were calculated for each individual as 1/PS for BAR2EVE or BAR4EVE and 1/(1 – PS) for BAR2MORN or BAR4MORN. A standardized mean difference (SMD) of < 0.1 was considered a negligible imbalance between groups [20]. Patients who discontinued treatment were included in the analysis and classified as having no response imputation (NRI). Continuous endpoint changes from baseline were analyzed using one-way analysis of variance (ANOVA) between BAR2EVE and BAR2MORN and BAR4EVE and BAR4 MORN after IPTW. The last observation carried forward (LOCF) method was used for missing data and patients who discontinued treatment. Changes in prednisolone (PSL) and MTX doses in each group were analyzed using the paired Wilcoxon signed-rank test. A two-sided *p*-value of < 0.05 was defined as significant. JMP Pro version 17 (SAS Institute Inc. Cary, NC, USA) was used for all analyses.

Results

Patient demographics

Overall, 122 patients were enrolled, of which 114 met the inclusion criteria and received at least one dose of the study drug. Of these, 93.0, 78.9, and 65.8% remained in the study up to weeks 12, 24, and 52, respectively (Fig. 1). Baseline patient characteristics are presented in Table 1. The participants in BAR4MORN tended to be younger than those in BAR4EVE; however, no other differences were observed in the background. Notably, the Japanese have low MTX tolerance, with a government-recommended maximum dose of 16 mg/week. As shown in Table 1, the initial MTX use was relatively low (72.4%, 53.3%, 59.3%, and 71.4%), with the initial MTX doses being 8.1 ± 2.8, 8.3 ± 2.4, 7.1 ± 2.5, and 8 ± 3.8 mg, respectively in each group.

To reduce selection bias, we adjusted for patient characteristics using IPTW (Table 2). In BAR4MORN vs. BAR4EVE, the MTX dose at baseline was slightly above an SMD of 0.1, whereas other characteristics were well balanced, including the rate of MTX use. In BAR2MORN vs. BAR2EVE, the rate of GC use, MTX use at baseline, PGA, and ESR were imbalanced with an SMD of 0.1–0.3, while other factors had SMD < 0.1.

Efficacy

The ACR20 response before IPTW was achieved in 76.7% of patients in BAR2EVE versus 55.2% in BAR2MORN and 78.6% in BAR4EVE versus 55.6% in BAR4MORN at week 12 (supplemental Figure S1). ACR20/50/70 for 52 weeks and DAS28 and CDAI changes before IPTW are presented in supplemental Figure S2. The results after adjusting for IPTW are as follows: primary endpoint was achieved in 78.2% of patients in BAR4EVE versus 43.3% in BAR4MORN ($p < 0.001$) and 75.5% in BAR2EVE versus 60.6% in BAR2MORN ($p = 0.10$) (Fig. 2A). The ACR20 response rate was significantly higher in BAR2EVE than in BAR2MORN at weeks 4 (72.4% vs. 45.4%), 24 (77.3% vs. 51.2%), and 52 (57.1% vs. 33.6%), and in BAR4EVE than in BAR4MORN at weeks 4 (70% vs. 31.8%), 8 (79.3% vs. 32.3%), and 12 (Fig. 2B). Further, the ACR50 response rate was significantly higher in BAR2EVE than in BAR2MORN at weeks 4 (40% vs. 15%) and 12 (55.6% vs. 29.6%), and in BAR4EVE than in BAR4MORN at weeks 4 (62.3% vs. 24.2%), 8 (70.7% vs. 24.7%), and 12 (72.6% vs. 33.1%) (Fig. 2C). Notably, the ACR70 response rate was significantly higher in BAR4EVE than in BAR4MORN at weeks 8 (54.9% vs. 2.4%), 12 (60.4% vs. 12.6%), and 24 (61.4% vs. 34.1%) (Fig. 2D).

ACR component changes from baseline were then evaluated. The SJC change significantly improved in BAR4EVE compared with BAR4MORN and in BAR2EVE compared with BAR2MORN throughout the 52-week period (Fig. 3A). Significant differences were observed in

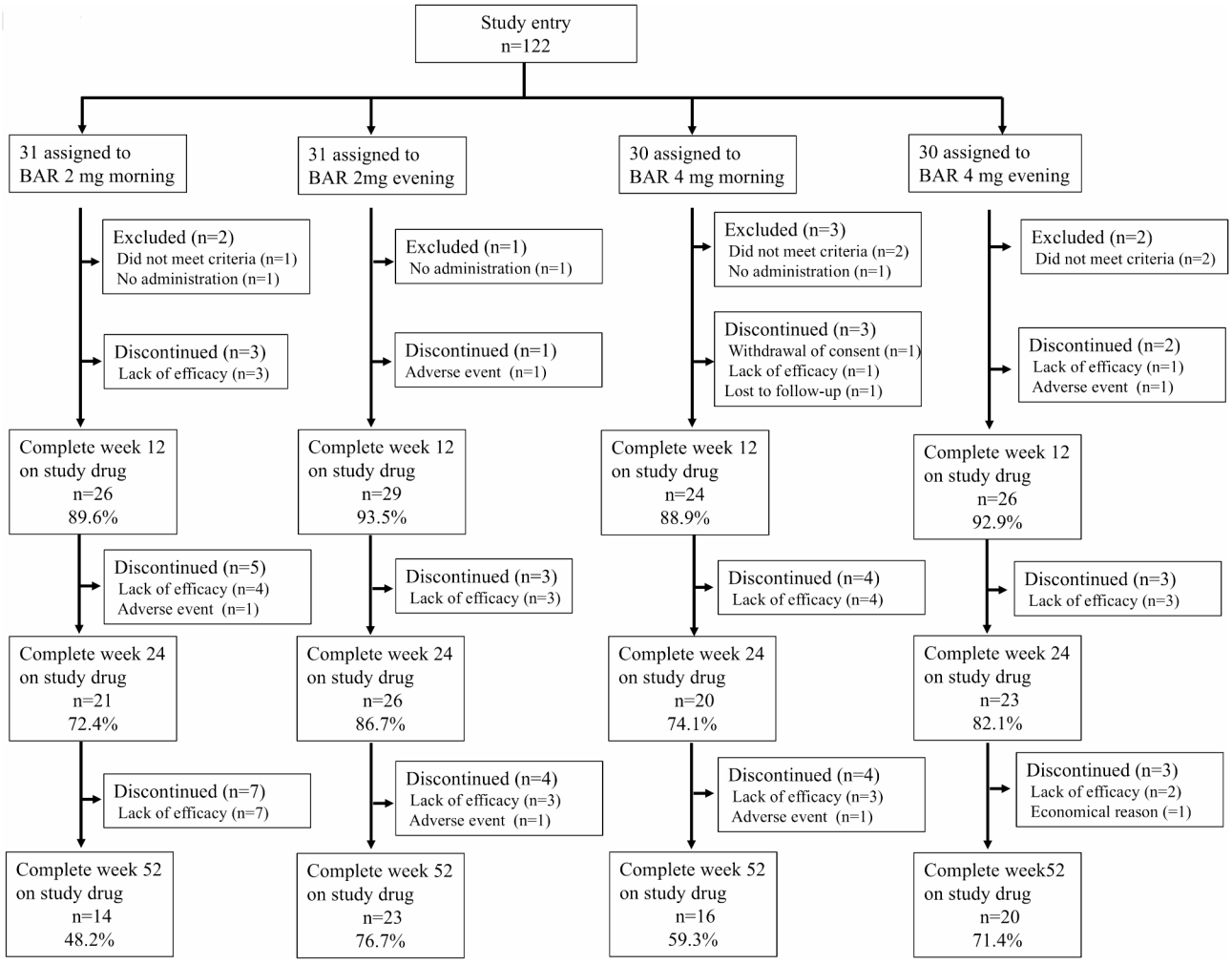

Fig. 1 Participant recruitment flow chart. BAR, baricitinib

pain and patient evaluation between BAR4EVE and BAR-4MORN; the change in TJC was greater in BAR4EVE at 4 and 8 weeks (Fig. 3B). Similarly, the change in PtGA at weeks 4 and 8 and patient pain at week 8 were greater in BAR4EVE (Fig. 3C and D). The change in PGA improved in BAR4EVE at week 4 (Fig. 3E). The change in HAQ-DI improved more in BAR4EVE than in BAR4MORN at week 52 (Fig. 3F). However, no inflammatory marker differences, including ESR and CRP, were observed in any group. (Figure 3G and H).

The change in DAS28-ESR improved in BAR4EVE compared with BAR4MORN at week 8 (Fig. 4A), with significant differences observed in remission rate between both groups at 12 and 24 weeks (Fig. 4B). Similarly, CDAI significantly improved at weeks 4 and 8 in BAR4EVE compared with BAR4MORN (Fig. 4C), with a significantly higher rate of patients achieving CDAI remission at weeks 12, 24, and 52 (Fig. 4D).

The MTX and PSL dose changes based on post-hoc analyses are presented in Fig. 5. The MTX dose was significantly decreased in BAR2EVE and BAR2MORN at weeks 24 and 52 compared with that at baseline. The PSL dose also decreased in BAR2EVE, BAR2MORN, and BAR4EVE groups at weeks 24 and 52 compared with that at baseline.

Safety

Adverse event incidences are presented in Table 3. TEAE incidences were 145.7/100, 140.6/100, 154.6/100, and 162.3/100 PY for BAR2MORN, BAR2EVE, BAR4MORN, and BAR4EVE, respectively. Serious adverse events included colon cancer and ischemic colitis in BAR2EVE, hyponatremia in BAR4MORN, and tuberculosis and pneumonia in BAR4EVE. Herpes zoster incidences were 10.1/100, 4.0/100, 5.2/100, and 4.4/100 PY for BAR-2MORN, BAR2EVE, BAR4MORN, and BAR4EVE, respectively. No major adverse cardiovascular event or venous thromboembolism was observed in any group. Adverse events leading to discontinuation included paresthesia in both legs in BAR2MORN, tongue paresthesia

Table 1 Patient characteristics before IPTW

	2 mg morning (*n* = 29)	2 mg evening (*n* = 30)	*P* value	4 mg morning (*n* = 27)	4 mg evening (*n* = 28)	*P* value
Age, years	65.5 ± 15.2	67.8 ± 10.9	0.85	57.5 ± 17.9	64.9 ± 15.7	0.09
Sex (male, female)	(2, 27)	(5, 25)	0.42	(3, 24)	(9, 19)	0.10
BMI, kg/m2	23.1 ± 4.6	22.6 ± 2.9	0.96	21.5 ± 3.8	22.7 ± 4.2	0.23
Disease duration, years	5 [1.1–12]	3.8 [0.8–9]	0.33	8 [2–16]	4.5 [1.8–12]	1
eGFR (mL/min)	61.5 ± 18.1	63.6 ± 13.8	0.83	72.1 ± 17.9	70.6 ± 11.2	0.65
Positive for RF- no (%)	26 (89.7)	21 (72.4)	0.18	25 (92.6)	23 (82.1)	0.42
Positive for ACPA - no (%)	20 (69.0)	24 (82.8)	0.36	24 (88.9)	22 (78.6)	0.25
MTX use at baseline - no (%)	21 (72.4)	16 (53.3)	0.18	16 (59.3)	20 (71.4)	0.40
MTX dose, mg/week	6 [0–10]	4 [0–8]	0.21	4 [0–8]	6 [0–10]	0.25
GC use at baseline - no (%)	14 (48.3)	15 (50)	1	15 (55.6)	16 (57.1)	1
Prednisolone dose, mg/day	0 [0–2.5]	1 [0–5]	0.21	1 [0–4]	2 [0–5]	0.65
Previous bDMARDs - no (%) (0/1/≧2)	18/8/3 (62.1/27.6/10.3)	18/9/3 (57.1/32.2/10.7)	1	13/8/6 (46.4/28.6/25.0)	9/14/5 (33.3/48.2/18.5)	0.36
66-Swollen joint count	3 [2–6]	4 [2.8–7]	0.77	3 [2–5]	3 [2–6.8]	0.59
68-Tender joint count	3 [2–6.5]	2.5 [1–4.3]	0.2	2 [1–4]	2 [1.3–6.8]	0.52
PtGA, VAS, mm	52 [32–79]	57.5 [29.8–73.5]	0.89	62 [49–79]	61.5 [37–86.3]	0.83
Patient pain, VAS, mm	48 [25.5–68]	50 [20.8–74.3]	0.85	63 [37–84]	63 [27.3–85.5]	0.68
PGA, VAS, mm	49 [35.5–64]	41.5 [33.5–53.5]	0.33	35 [22–55]	40 [31.5–55.3]	0.32
HAQ-DI	0.88 [0.25–1.5]	0.56 [0.22–1]	0.10	1.1 [0.25–1.75]	1 [0.28–1.97]	0.65
CRP, mg/L	6.1 [1–18.7]	16.8 [1.3–45.3]	0.16	9.1 [2.2–14.7]	4.2 [0.9–17.9]	0.61
ESR, mm/h	33 [15.5–61.5]	39 [27.3–87]	0.29	22[13–46]	19.5 [8.3–52]	0.48
DAS28-CRP	3.88 ± 0.89	3.96 ± 1.09	0.71	3.86 ± 0.86	4.01 ± 1.10	0.63
DAS28-ESR	4.61 ± 1.02	4.67 ± 1.05	0.67	4.37 ± 1.01	4.36 ± 1.43	0.87
CDAI	18.5 ± 6.1	18.0 ± 6.4	0.69	18.0 ± 9.8	20.6 ± 9.5	0.22
SDAI	19.8 ± 7.1	20.4 ± 8.3	0.82	18.9 ± 9.9	22.5 ± 11.2	0.26

Values are presented as the mean ± SD, median (interquartile range), or number of patients (n, %). IPTW: Inverse Probability of Treatment Weighted, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibodies, MTX: methotrexate, GC: glucocorticoid, bDMARDs: biological disease-modifying antirheumatic drugs, PtGA: patient global assessment, PGA: physician global assessment, HAQ-DI: Health Assessment Questionnaire-disability Index, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, DAS: Disease Activity Score, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index

and colon cancer in BAR2EVE, and tuberculosis in BAR4EVE.

Discussion

In this study comparing BAR2EVE versus BAR2MORN and BAR4EVE versus BAR4MORN, BAR4EVE achieved the better primary outcome of ACR20 response at week 12. Moreover, ACR20 improved at weeks 4, 24, and 52, with swollen joints significantly decreasing throughout week 52 in the 2 mg group after nighttime administration. Meanwhile, in the 4 mg group after nighttime administration, significant differences were observed in more precise indices, including ACR50, ACR70, and CDAI remission up to week 12; moreover, patient pain and HAQ-DI levels improved. A striking feature of nocturnal administration was the rapid drug response, reflected in the ACR response rate. When focusing on the T2T strategy within 12 weeks, BAR4EVE significantly outperformed BAR4MORN in all evaluations except ACR70 response rate at week 4 [21]. These results clearly indicate the effectiveness of chronotherapy using BAR.

Several studies have reported the significance of chronotherapy. Nighttime GC administration has been practiced for a long time, and its effectiveness was confirmed in an RCT in 2008 [11]. In this study, MR prednisone administration at night demonstrated a significant improvement in morning stiffness without threatening safety profile; however, no other indicators of RA disease status improvement apart from morning joint symptoms were observed [22]. Compared with these previous reports, our results demonstrate the high efficacy of chronotherapy with BAR based on various real-world endpoints. As a matter of fact, production of several cytokines such as IFNγ, IL-1/2/6/12 and TNF-α reach the peak during the night in the blood of RA patients [23]. BAR, a JAK1/2 inhibitor, is appeared to be more suitable for nocturnal administration than a selective JAK1 inhibitor because BAR covers not only IL-2/6/12 but also IFNγ. However, some cytokines have the potential to induce adverse events, including infections, through excessive suppression. We need to wait for the results of clinical studies of nocturnal administration with selective JAK inhibitors or broad JAKs inhibitors to confirm this.

BAR is metabolized in a short time. Therefore, we previously maximized the blood BAR concentration during cytokine elevation in the sera and demonstrated its effect

Table 2 Patient characteristics after IPTW

	2 mg morning (*n* = 50)	2 mg evening (*n* = 51)	*P* value	SMD	4 mg morning (*n* = 52)	4 mgevening (*n* = 53)	*P* value	SMD
Age, years	67.4 ± 19.3	67.6 ± 15.2	0.73	0.01	59.1 ± 21.7	56.5 ± 31.2	0.62	0.09
Sex (male, female)	(3, 47)	(5, 47)	0.49	0.06	(11, 41)	(12, 41)	0.85	0.04
Body mass index, kg/m2	23.2 ± 5.9	22.9 ± 3.8	0.81	0.06	22.6 ± 5.6	22.5 ± 6.6	0.95	0.01
Disease duration, years	6.8 ± 10.7	6.3 ± 8.3	0.77	0.06	9.3 ± 10.6	9.4 ± 12.9	0.95	0.01
eGFR (ml/min)	57.6 ± 24.7	62.8 ± 17.9	0.23	0.24	71.9 ± 25.5	69.9 ± 14.5	0.63	0.09
Positive for RF - no (%)	45 (91.2)	45 (88.2)	0.62	0.1	45 (86.7)	45 (83.4)	0.63	0.09
Positive for ACPA - no (%)	42 (84.4)	45 (87.7)	0.63	0.03	44 (84.8)	46 (85.3)	0.94	0.01
MTX use at baseline - no (%)	32 (64.0)	28 (54.4)	0.27	0.19	38 (74.4)	39 (73.4)	0.91	0.02
MTX dose, mg/week	4.9 ± 6.0	4.7 ± 6.6	0.86	0.03	5.2 ± 5.0	6.2 ± 6.2	0.36	0.18
GC use at baseline - no (%)	25 (49.7)	19(37.8)	0.23	0.24	26 (50.2)	24 (44.8)	0.59	0.1
Prednisolone dose, mg/day	1.6 ± 2.8	2.0 ± 4.2	0.59	0.1	2.0 ± 3.3	2.2 ± 3.0	0.75	0.06
Previous bDMARDs - no (%) (0/1/≧2)	32/13/5 (64.0/26.6/9.4)	32/15/4 (62.6/28.9/8.5)	0.96	0.03	19/20/13 (36.5/38.5/25)	21/22/10 (39.6/41.5/18.9)	0.71	0.06
66-Swollen joint count	4.6 ± 3.2	4.7 ± 3.2	0.96	0.02	4.6 ± 4.8	5.0 ± 4.7	0.64	0.07
68-Tender joint count	3.7 ± 3.8	3.5 ± 3.6	0.82	0.05	3.9 ± 5.2	4.2 ± 5.6	0.81	0.03
PtGA, VAS, mm	55.3 ± 36.0	55.5 ± 34.4	0.85	0.01	56.9 ± 36.3	55.3 ± 38	0.82	0.04
Patient pain, VAS, mm	50.0 ± 36.5	52.4 ± 36.6	0.60	0.06	55.8 ± 42.7	57.6 ± 38	0.82	0.04
PGA VAS, mm	49.8 ± 23.8	43.2 ± 23.6	0.16	0.28	38.5 ± 26	40.3 ± 20.4	0.69	0.07
HAQ-DI	0.81 ± 0.87	0.78 ± 0.92	0.96	0.03	0.98 ± 1.1	0.92 ± 1.2	0.78	0.05
CRP, mg/l	16.8 ± 26.6	20.1 ± 33.5	0.56	0.1	9.4 ± 1.1	12.7 ± 3.8	0.54	0.09
ESR, mm/h	46.5 ± 43.7	54.3 ± 50.0	0.32	0.16	27.6 ± 31.8	24.5 ± 32.4	0.62	0.09
DAS28-CRP	3.99 ± 1.37	3.86 ± 1.50	0.68	0.09	3.84 ± 1.24	3.76 ± 1.31	0.71	0.07
DAS28-ESR	4.77 ± 1.38	4.69 ± 1.51	0.87	0.06	4.25 ± 1.22	4.15 ± 1.73	0.74	0.06
CDAI	18.8 ± 8.8	18.0 ± 9.3	0.71	0.08	18.1 ± 12.6	18.8 ± 11.3	0.77	0.06
SDAI	20.4 ± 10.7	20.0 ± 11.8	0.89	0.03	19.0 ± 12.8	20.1 ± 13.1	0.69	0.08

Values are presented as the mean ± SD or number of patients (n, %). IPTW: Inverse Probability of Treatment Weighted, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibodies, MTX: methotrexate, GC: glucocorticoid, bDMARDs: biological disease-modifying antirheumatic drugs, PtGA: patient global assessment, PGA: physician global assessment, HAQ-DI: Health Assessment Questionnaire-disability Index, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, DAS: Disease Activity Score, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index

in CIA mice [12]. As BAR has a steady-state half-life of approximately 12.5 h [15], it can be administered after dinner (7–10 pm) to maintain blood levels until early morning, making it applicable in a realistic setting. In this regard, bDMARDs/bio-similars have relatively long half-lives and are not administered daily. Thus, it is important to maintain their blood concentrations for longer periods beyond the specified administration intervals.

In previous clinical trials, the ACR20/50/70 response rates with 4 mg BAR at 12 weeks were 69.6, 45, and 18.9%, respectively in RA-BEAM, and 55.4, 28.2, and 11.3%, respectively, in RA-BEACON [24, 25]. Our study was conducted in a real-world setting; therefore, our background was different from that of these trials, including patients with moderate disease activity and a mixture of bio-naïve and bio-switched patients. Therefore, we compared the results of our study with these studies by pooling in the 2 and 4 mg groups with and without chronotherapy, and the results were comparable to the ACR20/50/70 response rates of previous studies at 12 weeks: 66.1, 40.7, and 22.0%, respectively in the 2 mg group and 67.2, 56.3, and 38.2% in the 4 mg group.

Considering the effect of nighttime administration on adverse event incidence is also necessary. No increase was observed in adverse events with nighttime steroid administration in previous studies [11]. The overall number of adverse events was similar in all groups, approximately 35 per 100 PY. Notably, only two cases of serious infections, pneumonia and tuberculosis, were observed with BAR4EVE. Moreover, serious infections were observed at a rate of 8.8 per 100 PY. The rate of serious infection in the Japanese clinical trial was also 4.9 (4 mg) per 100 PY [26]. As presented in Fig. 5, GC reduction was possible with BAR4EVE throughout the 52-week observation period. This is particularly important for the prevention of herpes zoster, an infectious disease to be considered during JAK-I administration [27]. No evidence for evaluating changes in BAR blood concentration during sleep has been identified. The blood concentration of BAR as a single dose has a Tmax of 0.88 h and a serum concentration half-life of 6.85 h. In addition, approximately 60% is excreted in urine after 12 h and reaches a plateau after 24–48 h, suggesting that BAR is excreted in urine over a period of 1–2 days. Thus, it is unlikely that BAR blood concentration increases or that its half-life in

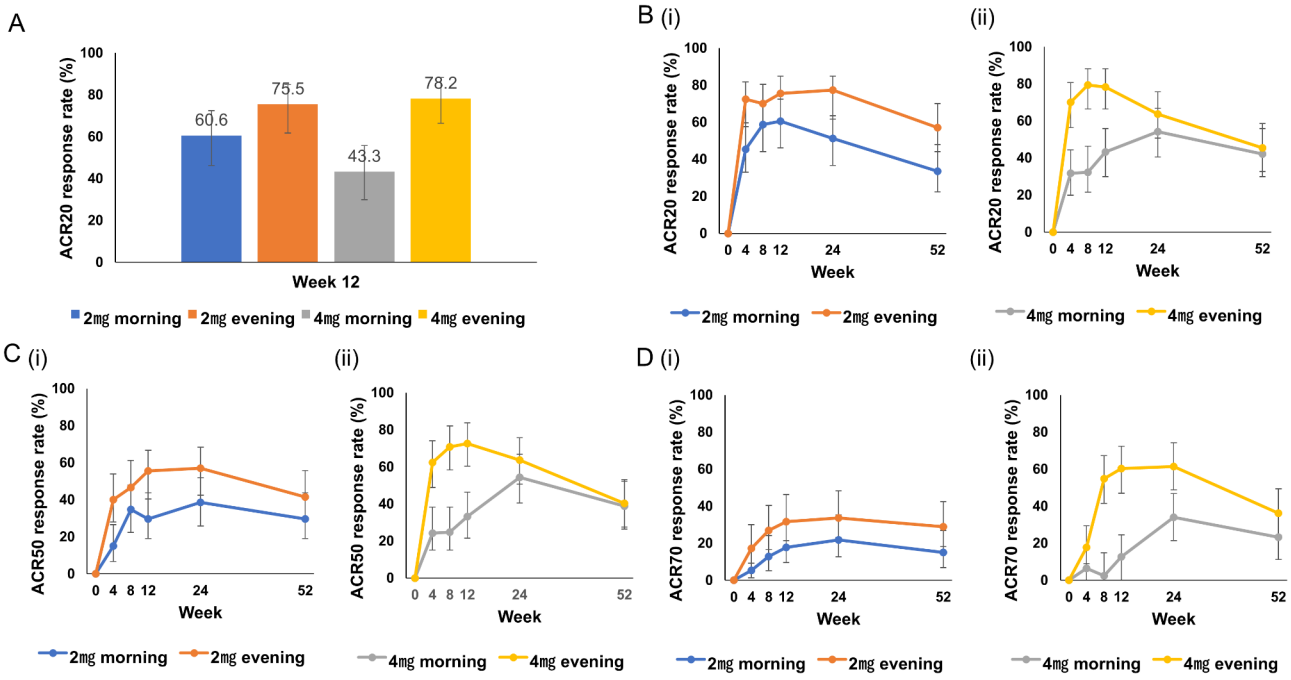

Fig. 2 Primary and secondary endpoints: (**A**) proportion of patients who achieved ACR20 at week 12. Baricitinib 4 mg in the evening resulted in better improvement than baricitinib 4 mg in the morning ($p < 0.001$). (**B**) Proportion of patients who achieved ACR20, (**C**) ACR50, and (**D**) ACR70 at weeks 4, 8, 12, 24, and 52. (i) Baricitinib 2 mg in the morning vs. baricitinib 2 mg in the evening, $n = 50, 51$ (ii) Baricitinib 4 mg in the morning vs. baricitinib 4 mg in the evening, $n = 52, 53$, respectively. Error bars represented a 95% confidence interval. ACR20, ACR50, and ACR70: 20%, 50%, and 70% improvement in American College of Rheumatology criteria

blood is prolonged during bedtime; moreover, the impact on renal function is considered insignificant. Our data showed no difference in creatinine at the beginning and end of the study. Immunosuppressive effects are unlikely to be enhanced with our chronotherapy regimen; however, this issue should be carefully examined in large-scale studies.

The limitations of this study are as follows. First, the confounding factors for all patients could not be adjusted, and the study was not randomized; therefore, unknown confounding factors may exist. Second, the study was conducted in a small number of Japanese patients and may not be applicable to patients with RA of all ethnicities. Third, as noted in the results, relatively few participants were administered MTX concomitantly owing to the low MTX tolerance in Japanese people. In addition, the imbalance in MTX dose between BAR4MORN and BAR4EVE is to be verified in the future.

Finally, the number of dropouts increased after the 24th week, and the results may have been influenced by the use of NRI and LOCF. As shown in Fig. 1, dropouts in the latter part of the study are mostly due to lack of efficacy. As this was a real-world study, decisions regarding treatment continuation were at the discretion of attending physicians; thus, some cases were discontinued if the drug was somewhat effective but did not achieve remission. Importantly, the drop-out rate could affect adverse event incidence, along with possible differences in efficacies.

Despite these limitations, improvement in drug efficacy at the same dose based on "administration time" has significant implications in real-world clinical practice and may also contribute to medical economics.

Conclusions

In summary, the ACR response and CDAI changes revealed that patients receiving chronotherapy responded more quickly to BAR than other patients, with most differences observed in the first half of the study (weeks 4 to 12). Moreover, patients undergoing chronotherapy had some advantages in clinical outcomes, including remission rates, from the early phase to the mid to late stages of the study. Notably, the high dose of 4 mg administered at night improved key indicators, including ACR70 and CDAI remission. Although confirmation by large-scale RCT is necessary, the efficacy of chronotherapy with BAR was demonstrated in a real-world setting, contributing to the growing body of literature on the management of rheumatic diseases.

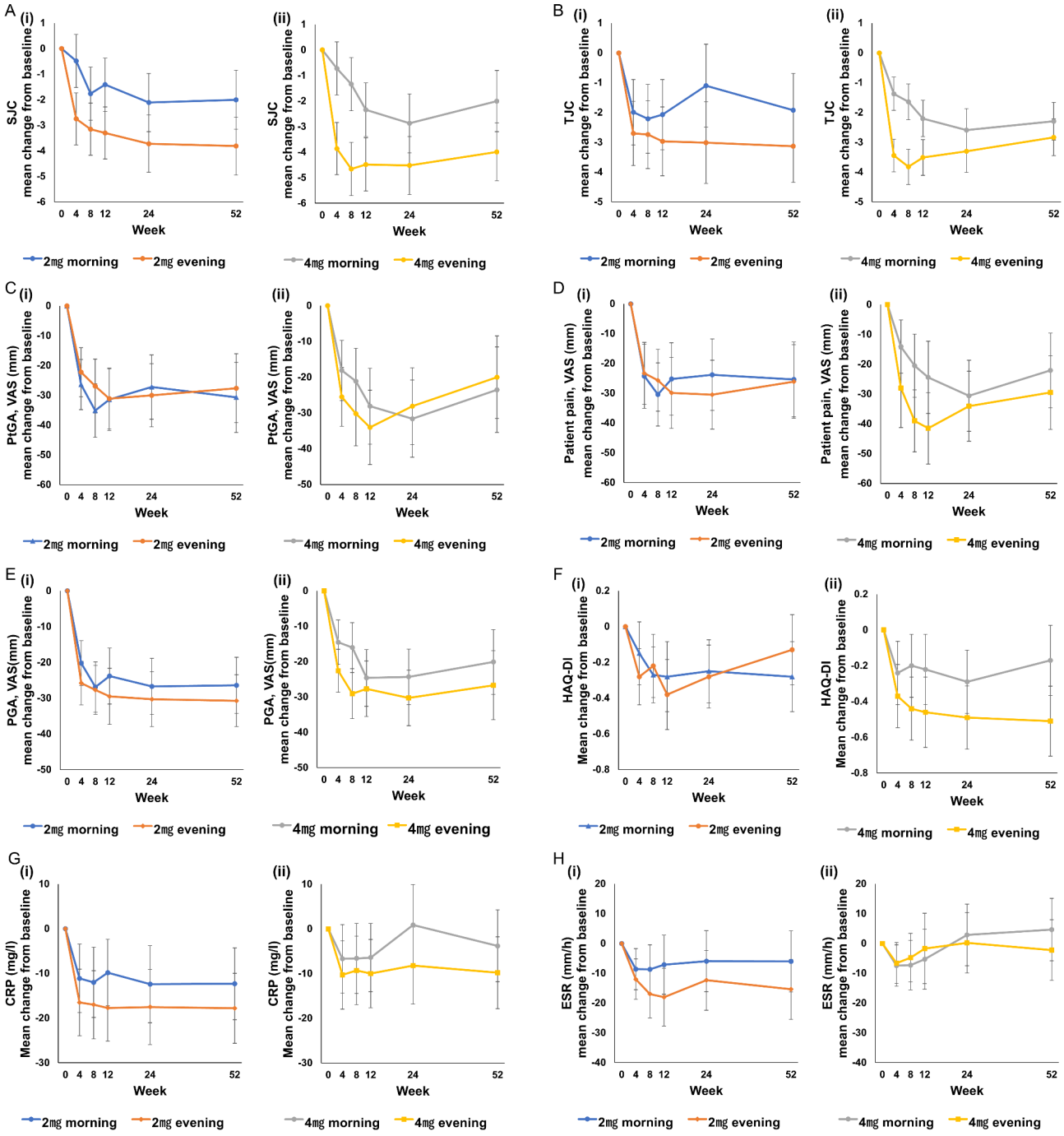

Fig. 3 Change in ACR components from baseline to weeks 4, 8, 12, 24, and 52: (**A**) SJC, (**B**) TJC, (**C**) PtGA VAS, (**D**) patient pain VAS, (**E**) PGA VAS, (**F**) HAQ-DI, (**G**) CRP, and (**H**) ESR. Results are presented as the mean ± 95% confidence interval: (**i**) baricitinib 2 mg in the morning vs. baricitinib 2 mg in the evening, $n = 50, 51$, (**ii**) baricitinib 4 mg in the morning vs. baricitinib 4 mg in the evening, $n = 52, 53$, respectively

Figure 4

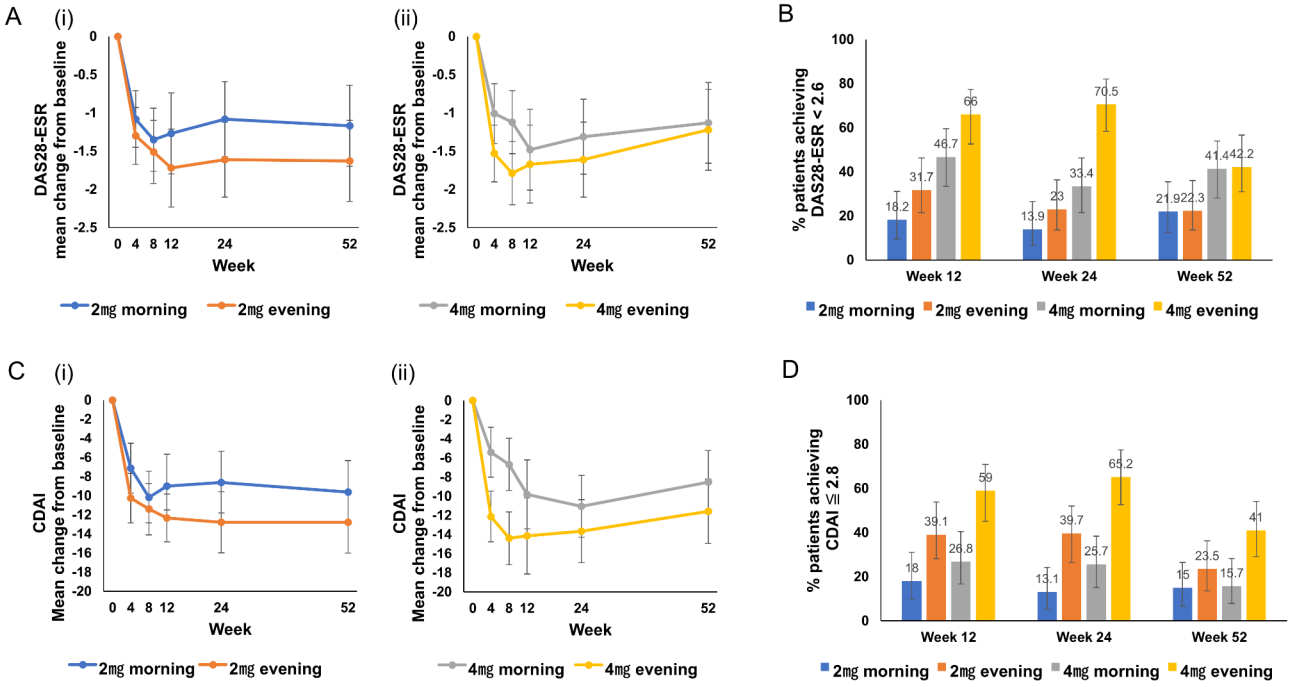

Fig. 4 Change in DAS28-ESR and CDAI from baseline to weeks 4, 8, 12, 24, and 52. DAS28-ESR (**A**) improved in baricitinib 4 mg in the evening compared with baricitinib 4 mg in the morning at week 8. Similarly, CDAI (**C**) significantly improved in baricitinib 4 mg in the evening at weeks 4 and 8. Results are presented as the mean ± 95% confidence interval. (**i**) Baricitinib 2 mg in the morning vs. baricitinib 2 mg in the evening $n = 50, 51$, (**ii**) Baricitinib 4 mg morning vs. baricitinib 4 mg in the evening, $n = 52, 53$, respectively. Proportion of patients achieving (**B**) DAS28-ESR < 2.6, (**D**) CDAI ≤ 2.8 at weeks 12, 24, and 52. Baricitinib 4 mg in the evening has a higher rate of patients achieving DAS28 remission at weeks 12 and 24 and CDAI remission at weeks 12, 24, and 52. Error bars represented 95% confidence interval; $n = 50, 51, 52$, and 53 for baricitinib 2 mg in the morning, 2 mg in the evening, 4 mg in the morning, and 4 mg in the evening, respectively

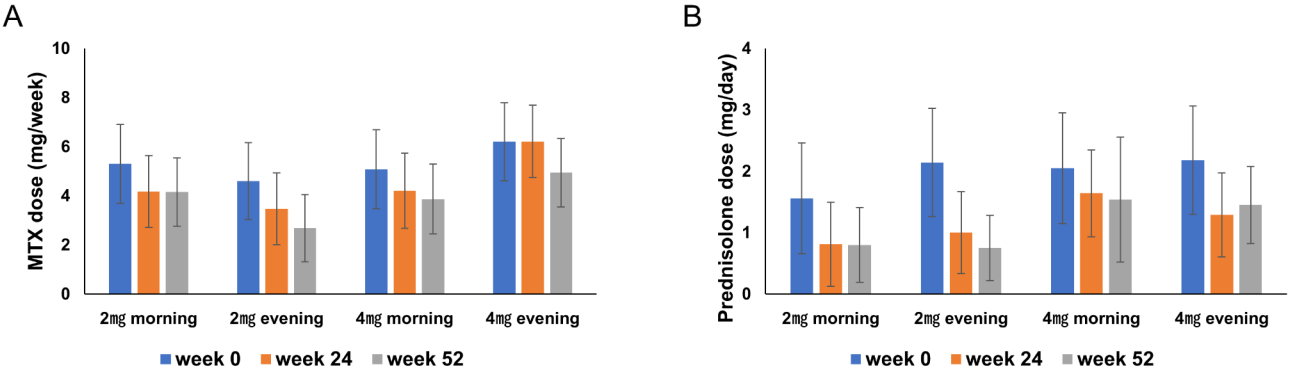

Fig. 5 MTX (**A**) and prednisolone (**B**) doses at weeks 0, 24, and 52. MTX dose was significantly decreased in baricitinib 2 mg in the evening and 2 mg in the morning groups at weeks 24 and 52 as compared with baseline. The prednisolone dose also decreased in baricitinib 2 mg in the morning, baricitinib 2 mg in the evening, and baricitinib 4 mg in the evening groups at weeks 24 and 52 as compared to that at the baseline. Results are expressed as the mean ± 95% confidence interval; $n = 50, 51, 52$, and 53 for baricitinib 2 mg baricitinib in the morning, 2 mg in the evening, 4 mg in the morning, and 4 mg in the evening, respectively, paired Wilcoxon signed-rank test

Table 3 TAEAs through 52 weeks

	2 mg morning (*n* = 29, PY 19.9) E (E/100 PY)	**2 mg evening (*n* = 30, PY 24.9) E (E/100 PY)**	**4 mg morning (*n* = 27, PY 19.4) E (E/100 PY)**	**4 mg evening (*n* = 28, PY 22.8) E (E/100 PY)**
Any TEAE	29 (145.7)	35 (140.6)	30 (154.6)	37 (162.3)
Serious TEAE	0 (0)	2 (8.0)	1 (5.2)	2 (8.8)
TEAE leading to discontinuation of study drug	1 (5.0)	2 (8.0)	0	2 (8.8)
Death	0	0	0	0
TEAEs of special interest				
Infection	5 (25.1)	5 (20.1)	8 (41.2)	11 (48.2)
Serious infection	0	0	0	2 (8.8)
Herpes zoster	2 (10.1)	1 (4.0)	1 (5.2)	1 (4.4)
Active TB	0	0	0	1 (4.4)
Malignancy	0	1 (4.0)	0	0
Adjudicated MACEs	0	0	0	0
Adjudicated VTE	0	0	0	0
CPK elevation	5 (25.1)	5 (20.1)	5 (25.8)	6 (26.3)
Anemia (Hb < 110 g/L)	5 (25.1)	5 (20.1)	3 (15.5)	7 (30.7)
Hb change from baseline				
Grade 3 (decrease 21–29 or Hb ≥ 70 to < 80 g/L)	1 (5.0)	0	3 (15.5)	1 (4.4)
Grade 4 (decrease 30 or Hb < 70 g/L)	1 (5.0)	1	0	0
Lymphopenia (< 1,000 /μL)	4 (20.1)	6 (24.1)	6 (30.9)	5 (21.9)
Neutropenia (< 1,000 /μL)	0	0	0	1 (4.4)
Hepatic disorder*	4 (20.1)	4 (16.1)	5 (25.8)	5 (21.9)
Renal dysfunction†	1 (5.0)	0	0	1 (4.4)

Values are presented as number of patients (n/100 person-years). TAEA, treatment-emergent adverse events; TB, tuberculosis; MACEs, major adverse cardiovascular events; VTE, venous thromboembolism; CPK, creatine phosphokinase; Hb, hemoglobin

* Hepatic disorder defined as alanine aminotransferase (ALT) elevation from baseline and > upper limit of normal

†Renal dysfunction defined as creatinine elevation from baseline and > upper limit of normal

Abbreviations

ACR	American College of Rheumatology
BAR	Baricitinib
BAR2MORN	BAR 2 mg morning
BAR2EVE	BAR 2 mg evening
BAR4MORN	BAR 4 mg morning
BAR4EVE	BAR 4 mg evening
bDMARDs	Biological disease-modifying antirheumatic drugs
CDAI	Clinical Disease Activity Index
CIA	Collagen-induced arthritis
DAS28	Disease Activity Score 28
GC	Glucocorticoid
HAQ-DI	Health Assessment Questionnaire-disability Index
IL-6	Interleukin-6
IPTW	Inverse probability of treatment weighted
IQR	Interquartile range
JAK-I	Janus kinase inhibitors
LOCF	Last observation carried forward
MTX	Methotrexate
NRI	No response imputation
PGA	Physician global assessment
PS	Propensity score
PSL	Prednisolone
PtGA	Patient global assessment
RA	Rheumatoid arthritis
RCT	Randomized Controlled Trial
SD	Standard deviation
SJC	Swollen joint count
SMD	Standardized mean difference
TAEAs	Treatment-emergent adverse events
TJC	Tender joint count
TNF	Tumor necrosis factor

Supplementary Information

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Supplementary Material 1

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Author contributions

TH and AH designed the study. KT, TA, TY (Takahiro Yoshikawa), KN, TF, KT, YT, NS, and KM collected clinical data. NA and TY (Takashi Yamane) provided scientific advice. All authors contributed to writing the manuscript and agree to the contents.

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Data availability

The raw data for this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committees of Hyogo Medical University, Kobe City Medical Center West Hospital, Konan (Hakuhoukai), Kakogawa Hospital, and Kobe Kaisei Hospital. All participants signed informed consent forms.

Consent for publication
Not applicable.

Competing interests
AH: Honoraria from AbbVie G.K., and honoraria and grants from Eli Lilly Japan K.K., Asahikasei Pharma Co. and Chugai Pharmaceutical Co. TY (Takashi Yamane): Honoraria from GlaxoSmithKline K.K. KM: Grants from Asahikasei Pharma Co. and Chugai Pharmaceutical Co. The other authors: No conflicts of interest.

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