ORIGINAL ARTICLE

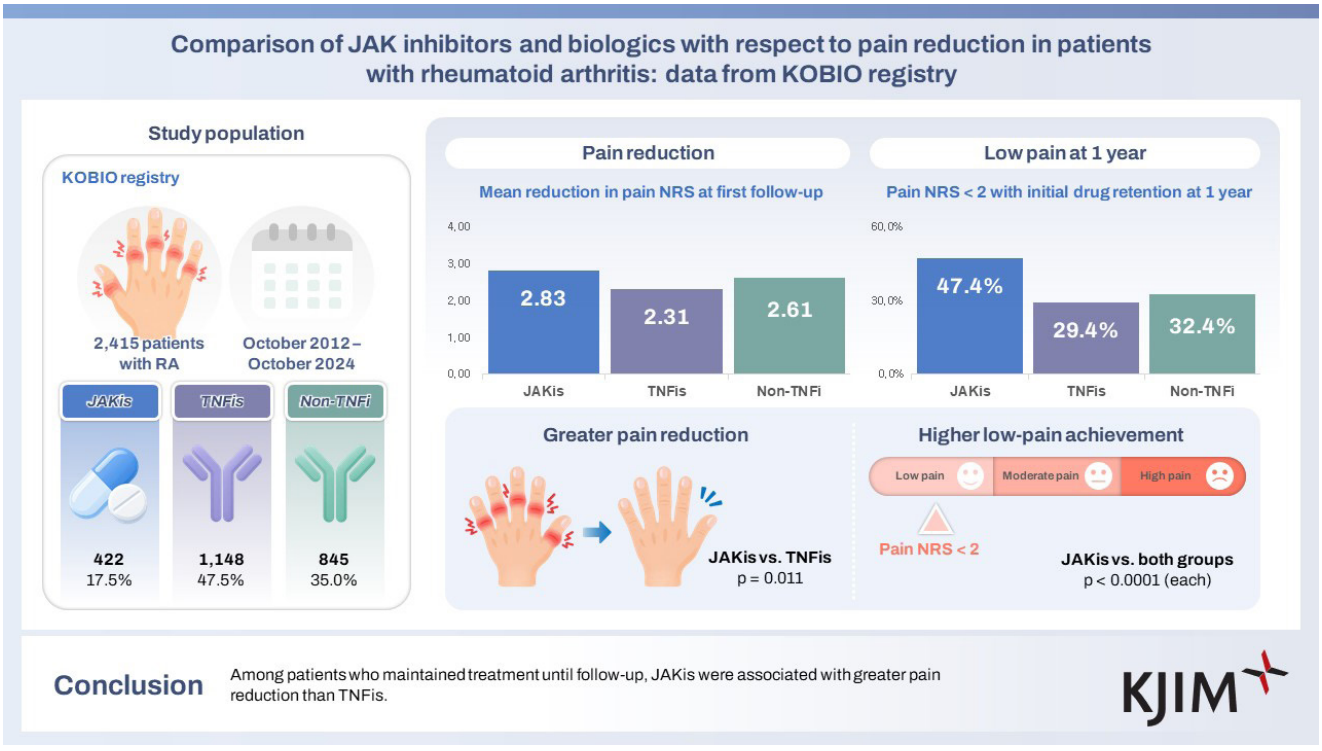
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KJIM

Comparison of JAK inhibitors and biologics with respect to pain reduction in patients with rheumatoid arthritis: data from the KOBIO registry

Howook Jeon[1] and Hong Ki Min[2]

[1]Division of Rheumatology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [2]Division of Rheumatology, Department of Internal Medicine, Research Institute of Medical Science, Konkuk University School of Medicine, Seoul, Korea



Background/Aims: To compare the pain-reducing efficacy of Janus kinase inhibitors (JAKis) and biologic disease-modifying antirheumatic drugs (bDMARDs) in patients with rheumatoid arthritis (RA).

Methods: Patients with RA enrolled in the Korean College of Rheumatology Biologics and Targeted Therapy (KOBIO) registry were grouped according to use of JAKis, TNFis, and non-TNFi bDMARDs. The primary outcome was to compare the changes in pain on a numeric rating scale (NRS, range 0–10) between enrolment and first follow-up. Logistic regression analysis was performed to identify the factors associated with a low pain NRS score (< 2) and retention at the 1-year follow-up.

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Results: The analysis included 2,415 patients with RA in the JAKis (n = 422), TNFis (n = 1,148), and non-TNFi bDMARDs groups (n = 845). The change in pain NRS was significantly greater in the JAKis group than in the TNFis group (2.8 ± 2.5 *vs.* 2.3 ± 2.9, respectively; $p < 0.01$). The adjusted mean additional pain reduction was significantly greater in the JAKis than in the TNFis group (–0.42, 95% confidence interval [CI]: –0.73 to –0.10). The adjusted odds ratio (OR) for achieving a pain NRS score < 2 with initial drug retention at 1 year follow-up was significantly lower in the TNFis (OR = 0.515; 95% CI: 0.406–0.652) and non-TNFi bDMARDs (OR = 0.586; 95% CI: 0.458–0.751) groups than in the JAKis group.
Conclusions: Among patients who achieved treatment response and remained on therapy, JAKis were associated with greater improvement in pain control than TNFis.

Keywords: Rheumatoid arthritis; Pain; Janus kinase inhibitor; Biologics; Cohort study

INTRODUCTION

Recent guidelines recommend the use of Janus kinase inhibitors (JAKis), which are targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), to treat patients with rheumatoid arthritis (RA) in whom disease activity is uncontrolled even after sufficient treatment with conventional synthetic DMARDs (csDMARDs) [1,2]. In contrast to biologic DMARDs (bDMARDs), which suppress specific cytokine- or cell surface molecule-mediated signals, JAKis suppress intracellular signals mediated by the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway [3]. Therefore, bDMARDs and JAKis can cause various adverse events [4-6]. Treat-to-target RA, which aims to achieve low disease activity or remission, requires the active use of JAKis or bDMARDs [1,2]. In the real world, the addition of csDMARDs, starting with bDMARDs, switching bDMARDs, and/or changing to JAKis, has been attempted to achieve treat-to-target response in RA patients [7].

The pain mechanism(s) associated with RA are not limited to nociception [8], and remnant pain after disease remission is problematic [9,10]. A nationwide observational study showed that 25.1% of RA patients who achieved remission after ts/bDMARD therapy complained of moderate-to-severe pain [9]. The International Association for the Study of Pain suggests that there are three types of pain: 1) nociceptive, 2) neuropathic, and 3) nociplastic, and states that the pain continuum is mediated via complicated mechanisms that play roles in RA-related pain [11,12]. Evaluating pain severity is a key component of the regular assessment of patients with RA [13]. A post hoc analysis of baricitinib and a nationwide observational study demonstrated that JAKis reduced pain more effectively than bDMARDs [14,15].

In this study, we evaluated data from the Korean College of Rheumatology Biologics and Targeted Therapy (KOBIO) registry to compare the degree of pain reduction in patients with RA receiving JAKis or bDMARDs. In addition, we performed subgroup analysis and propensity score (PS) matching to validate the results. Finally, we evaluated the factors associated with low pain levels at 1-year follow-up.

METHODS

Study population

Data from patients with RA who started or restarted tsDMARDs (JAKis) or bDMARDs and were enrolled in the KOBIO registry from October 2012 to October 2024 were analyzed (ClinicalTrials.gov identifier NCT01965132). Patients who fulfilled the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for RA [16], and were older than 18 years were enrolled in the KOBIO registry. Patients whose data were collected at least once during the follow-up were included in the analyses. Follow-up data were collected at least once annually, usually at one-year intervals, but records earlier than one-year intervals could occur when the initial b/tsDMARD was stopped due to inefficacy or adverse events. The exclusion criteria were as follows: 1) patients who withdrew consent for enrolment, 2) patients who did not have follow-up data, and 3) patients who lacked pain numerical rating scale (NRS) data at baseline or follow-up. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good

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Clinical Practice guidelines, and was approved by the institutional review boards of each participating hospital (IRB number: KUMC 2022-06-005). All patients provided written informed consent prior to enrolment.

Data collection and outcomes

Baseline demographics, laboratory data, treatments, comorbidities, health-and daily function-related self-rated scales (EuroQol-Visual Analog Scale, RAPID3) [17,18], and disease-related parameters, including the disease activity score-28 joint (DAS28) [19], simplified disease activity index for RA (SDAI) [20], and clinical disease activity index for RA (CDAI) [21], were collected at the time of consent to participate in the KOBIO registry. The pain NRS scores ranged from 0 to 10. The first follow-up data (follow-up pain NRS score) were collected at the 1-year follow-up in cases of continuing the initial ts/bDMARDs or when the initial ts/bDMARDs were stopped or switched to another agent owing to adverse events or inefficacy. The treatment choice was decided by the treating physician at each hospital, and the patients with RA were divided into three groups: 1) JAKis users, 2) tumor necrosis factor inhibitors (TNFis) users, and 3) non-TNFi bDMARDs (abatacept, tocilizumab, or rituximab) users. The primary outcome was the degree of reduction in pain NRS score at the first follow-up. The secondary outcome was the achievement of a pain NRS score of < 2 while maintaining the initial therapy at the 1-year follow-up. Switching to other ts/bDMARDs or discontinuation due to adverse events was considered discontinuation, whereas discontinuation of the initial ts/bDMARDs due to remission was considered continuation. As the exclusion of patients who discontinued before the 1st follow-up visit or were lost to follow-up could lead to selection bias, the response measure at the 1-year follow-up was defined as the percentage of patients who reported low pain (pain NRS < 2) levels while remaining on therapy (LUNDEX-corrected response) [22]. The cut-off value for low pain (pain NRS < 2) was defined as the minimal disease activity of RA [23].

Statistical analyses

Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are expressed as counts and percentages. Differences in continuous outcomes among the treatment groups were assessed using one-way analysis of variance (ANOVA). When the ANOVA *p* value was significant, pairwise group comparisons were performed using the Tukey's honest significant difference test. The Bonferroni correction was applied to adjust for multiple comparisons. Subgroup analyses were performed based on ts/bDMARD-naïve versus-experienced status. Within each subgroup, ANOVA and pairwise comparisons were repeated to assess the consistency of treatment effects across strata. In addition, to reduce the potential confounding factors in the observational comparisons, pairwise PS matching was conducted for the JAKis *vs.* TNFis and JAKi *vs.* non-TNFi bDMARDs groups. PS was estimated using logistic regression, incorporating age, sex, disease duration, and ts/bDMARD naïve status as covariates. A 1:1 nearest-neighbor matching without replacement was applied based on the estimated PS. Covariate balance before and after matching was evaluated using standardized mean differences (SMDs) and visualized using Love plots. PS distribution plots were used to assess the overlap between groups. After matching, two-sample t-tests were used to compare changes in pain NRS scores between the matched groups. Univariate and multivariate logistic regression models were fitted to evaluate the association between the treatment groups and binary outcomes of pain NRS score < 2 with initial drug retention at the 1-year follow-up. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Factors that showed a *p* value < 0.05 in univariate logistic regression analysis were entered into the multivariable model. Statistical significance was defined as a two-sided *p* value of < 0.05. All statistical analyses were performed using Python (v3.11), with the statistical models SciPy and Sklearn libraries. As the outcome assessment depended on the availability of the first follow-up data and treatment retention, the present analysis should be interpreted as a treatment-retention-based observational analysis rather than a strict intention-to-treat comparison.

RESULTS

Baseline characteristics of enrolled RA patients

A total of 2,415 patients with RA who met the inclusion and exclusion criteria were included in the analysis (Fig. 1). The number of patients with RA in the TNFis group was 1,148 (etanercept = 322, adalimumab = 433, infliximab = 225, golimumab = 168), that in the non-TNFi bDMARDs group was 845 (tocilizumab = 541, abatacept = 284, rituximab = 20), and that in the JAKis group was 422 (tofacitinib =

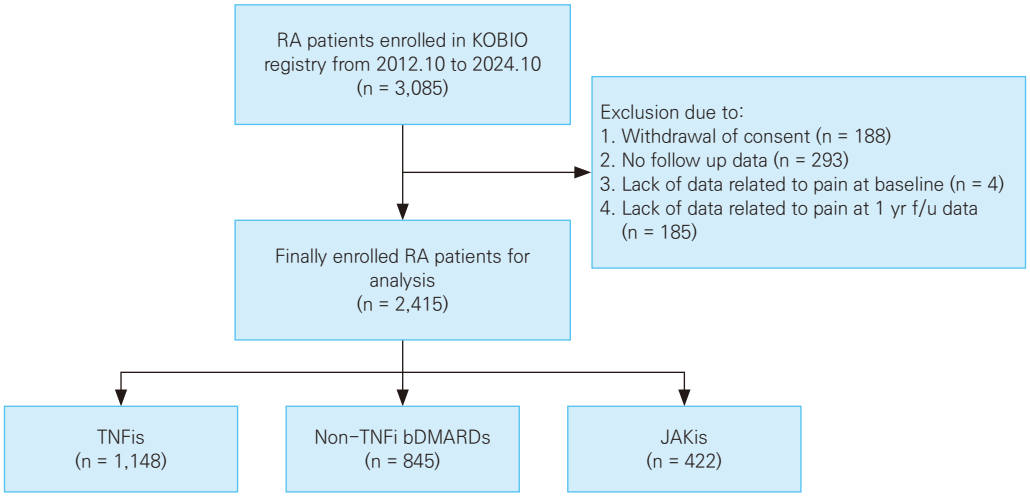


Figure 1. Flowchart showing enrolment of patients with rheumatoid arthritis (RA). KOBIO, Korean College of Rheumatology Biologics and Targeted Therapy; TNFis, tumor necrosis factor inhibitors; JAKis, janus kinase inhibitors; bDMARDs, biologic disease-modifying antirheumatic drugs.

176, baricitinib = 153, upadacitinib = 93). The male-to-female ratio was comparable among the three groups, with a predominance of females. At baseline, we found significant differences between the treatment groups with respect to several variables, including age ($p < 0.001$), disease duration ($p = 0.003$), pain NRS score ($p < 0.001$), percentage of ts/bDMARD-naïve patients ($p < 0.001$), and disease activity scores DAS28-ESR, DAS28-CRP, SDAI, and CDAI ($p < 0.001$ for all). Tukey's post-hoc test revealed that patients in the TNFis group were significantly younger than those in the JAKis and non-TNFi bDMARDs groups ($p = 0.007$ for TNFis *vs.* JAKis; $p < 0.001$ for TNFis *vs.* non-TNFi bDMARDs). The percentage of ts/bDMARD-naïve patients in the TNFis group was significantly higher than that in the JAKis and non-TNFi bDMARDs groups ($p = 0.02$, TNFis *vs.* JAKis; $p < 0.001$, TNFis *vs.* non-TNFi bDMARDs). Pain NRS scores were significantly lower in the JAKis group than in the TNFis and non-TNFi bDMARDs groups ($p = 0.026$ for JAKis *vs.* TNFis; $p < 0.001$ for JAKis *vs.* non-TNFi bDMARDs). Similar trends were observed for other patient-reported outcomes (patient global assessment and RAPID3 score) and erythrocyte sedimentation rate (ESR). The baseline characteristics are summarized in Table 1, and detailed pairwise post hoc comparison results for the baseline characteristics are summarized in Supplementary Table 1.

Comparison of the level of pain reduction between RA patients treated with JAKis, TNFis, or non-TNFi bDMARDs

The mean follow-up duration in the JAKis group was longer than that in the TNFis group or the non-TNFi bDMARDs group (mean ± SD of follow-up duration: 10.35 ± 7.27 months for TNFis group, 11.02 ± 7.14 months for non-TNFi bDMARDs group, and 13.32 ± 12.62 months for JAKis group, Supplementary Fig. 1). The reduction in the pain NRS at first follow-up was significantly greater in the JAKis group than in the TNFis group (2.83 ± 2.54 *vs.* 2.31 ± 2.92, $p = 0.011$). The difference in the degree of change in the pain NRS scores between the JAKis and non-TNFi bDMARDs groups was not significant. The adjusted mean change in pain NRS across the treatment groups was compared using multivariable linear regression, with the JAKis group as the reference. After adjusting for age, sex, disease duration, follow-up duration, and whether the patient was ts/bDMARD-naïve, patients in the TNFis group demonstrated significantly less improvement in the pain NRS than those receiving JAKis (adjusted mean difference: -0.42, 95% CI: -0.73 to -0.10). The non-TNFi bDMARDs group also showed a numerically smaller change, although the difference did not reach statistical significance (adjusted mean difference: -0.09, 95% CI: -0.42 to 0.25, Table 2). Subgroup analyses were performed using ts/bDMARD-naïve (n = 1,855 [TNFis = 960, non-TNFi bDMARDs = 573, JAKis = 322]) and t/bDMARD-experienced (n = 560 [TNFis = 188, non-TNFi

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Table 1. Baseline characteristics of the enrolled patients

Variable	JAKis group (N = 422)	Non-TNFi bDMARDs group (N = 845)	TNFis group (N = 1,148)	*p* value
Female	345 (81.8)	707 (83.7)	947 (82.5)	0.655
Age (yr)	55.4 ± 11.5	56.2 ± 13.0	53.0 ± 13.1	< 0.001
Disease duration (yr)	8.2 ± 7.4	8.2 ± 7.5	7.2 ± 7.3	0.003
BMI (kg/m^2)	22.9 ± 3.5	22.7 ± 3.4	22.8 ± 3.5	0.405
ts/bDMARD-naïve	322 (76.3)	573 (67.8)	960 (83.6)	< 0.001
Smoking status				0.051
Ex-smoker	25 (5.9)	84 (9.9)	105 (9.1)	
Current smoker	45 (10.7)	61 (7.2)	93 (8.1)	
Never smoker	352 (83.4)	700 (82.8)	950 (82.8)	
Comorbidities				
Diabetes mellitus	53 (12.6)	103 (12.2)	131 (11.4)	0.777
Hypertension	127 (30.1)	275 (32.5)	320 (27.9)	0.079
Dyslipidemia	104 (24.6)	208 (24.6)	225 (19.6)	0.012
Migraine	2 (0.5)	0	6 (0.5)	0.067
Osteoporosis	76 (18.0)	270 (32.0)	242 (21.1)	< 0.001
Hyperthyroidism	3 (0.7)	11 (1.3)	15 (1.3)	0.596
Hypothyroidism	24 (5.7)	40 (4.7)	61 (5.3)	0.739
CKD	3 (0.7)	19 (2.2)	14 (1.2)	0.060
MDD	9 (2.1)	18 (2.1)	26 (2.3)	0.975
Malignancy	1 (0.2)	6 (0.7)	2 (0.2)	0.140
Swollen joint count (0–44)	5.3 ± 3.9	6.4 ± 5.2	6.9 ± 5.7	< 0.001
Tender joint count (0–44)	6.8 ± 5.1	8.5 ± 6.4	9.0 ± 7.2	< 0.001
Patient's global assessment (0–10)	6.3 ± 2.0	7.0 ± 2.0	6.7 ± 2.0	< 0.001
Physician's global assessment (0–10)	6.2 ± 1.7	6.5 ± 1.8	6.4 ± 1.8	0.018
ESR (mm/hr)	45.7 ± 29.4	51.0 ± 28.3	47.2 ± 27.4	0.001
hs-CRP (mg/dL)	2.1 ± 4.6	2.3 ± 3.0	2.0 ± 2.6	0.156
DAS28-ESR	5.2 ± 1.1	5.6 ± 1.1	5.5 ± 1.2	< 0.001
DAS28-CRP	4.5 ± 1.1	4.9 ± 1.1	4.8 ± 1.2	< 0.001
SDAI	25.4 ± 10.4	29.3 ± 11.5	28.7 ± 12.0	< 0.001
CDAI	23.3 ± 8.9	27.0 ± 10.8	26.6 ± 11.4	< 0.001
Pain NRS (0–10)	5.8 ± 2.2	6.3 ± 2.2	6.2 ± 2.2	< 0.001
RAPID3	14.0 ± 5.5	15.6 ± 5.7	14.9 ± 5.5	< 0.001
EQ-VAS	5.4 ± 2.1	5.9 ± 2.2	5.6 ± 2.0	0.112
RF positive	321 (79.7)	676 (83.9)	913 (82.3)	0.192
ACPA positive	321 (87.7)	613 (85.9)	804 (85.0)	0.449

Data are presented as the mean ± standard deviation or as numbers (%).
Group differences were assessed using one-way ANOVA.
Post-hoc pairwise comparisons were performed using Tukey's test with Bonferroni adjustment.
Detailed pairwise comparison results are presented in Supplementary Table 1.
JAKis, janus kinase inhibitors; TNFis, tumor necrosis factor inhibitors; BMI, body mass index; ts/bDMARDs, targeted synthetic/biologic disease-modifying antirheumatic drugs; CKD, chronic kidney disease; MDD, major depressive disorder; ESR, erythrocyte sedimentation rate; hs-CRP, high sensitive C-reactive protein; DAS28, disease activity score 28 joints; SDAI, simplified disease activity index; CDAI, clinical disease activity index; NRS, numeric rating scale; RAPID3, routine assessment of patient index data 3; EQ-VAS, EuroQol-visual analogue scale; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody.

Table 2. Baseline pain NRS scores and mean changes at first follow-up

Treatment	N	Baseline mean pain NRS (0–10)	Mean change of pain NRS (baseline–first f/u)	Crude change contrast	Adjusted change contrast
TNFis	1,148	6.17 ± 2.19	2.31 ± 2.92	-0.52 (-0.84 to -0.20)	-0.42 (-0.73 to -0.10)
Non-TNFi bDMARDs	845	6.32 ± 2.20	2.61 ± 2.87	-0.22 (-0.55 to 0.11)	-0.09 (-0.42 to 0.25)
JAKis	422	5.79 ± 2.22	2.83 ± 2.54	Ref	Ref

Values are presented as the mean ± standard deviation.
Differences in the mean change in the pain NRS were evaluated using linear regression. Crude and adjusted changes (with 95% confidence intervals) are shown for each group (compared with the JAKis reference group).
Adjusted estimates were derived from multivariable models controlled for age, sex, disease duration, follow up duration, and prior exposure to ts/bDMARDs. Negative values indicate less improvement in the pain NRS (compared with the JAKis group).
NRS, numerical rating scale; TNFis, tumor necrosis factor inhibitors; JAKis, janus kinase inhibitors; ts/bDMARDs, targeted synthetic/biologic disease-modifying antirheumatic drugs.

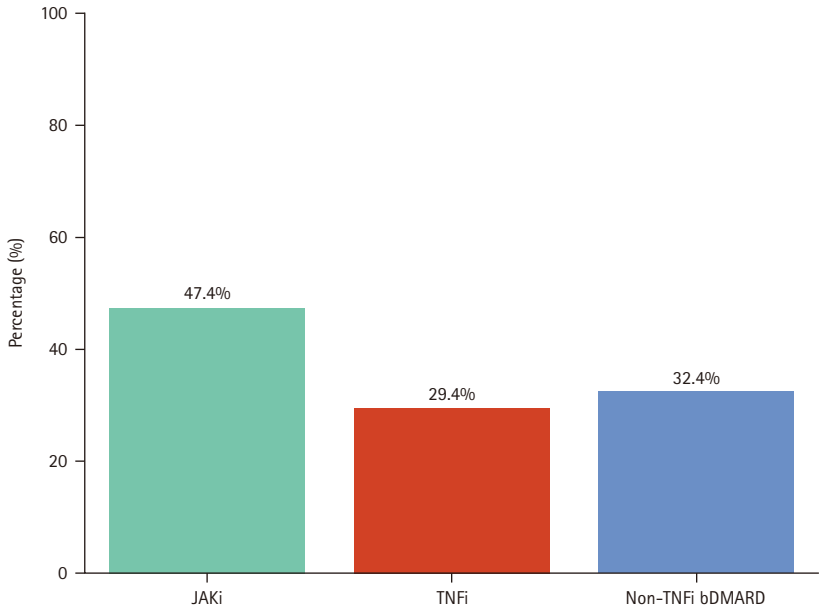
Table 3. Baseline pain NRS scores and mean changes at first follow-up across treatment groups after propensity score matching

Group	N	Baseline mean pain NRS (0–10)	Mean change of pain NRS (baseline–first f/u)	Crude change contrast
PS matching between TNFis and JAKis group				
TNFis	422	6.11 ± 2.23	2.14 ± 2.87	-0.67 (-1.03 to -0.30)
JAKis	422	5.79 ± 2.22	2.83 ± 2.54	Ref
PS matching between non-TNFi bDMARDs and JAKis group				
Non-TNFi bDMARDs	422	6.30 ± 2.28	2.58 ± 2.83	-0.25 (-0.61 to 0.11)
JAKis	422	5.79 ± 2.22	2.83 ± 2.54	Ref

Values are presented as the mean ± standard deviation.
Comparison of the pain NRS and changes in the pain NRS after propensity score matching was made between treatment groups.
Pairwise matching was performed for the JAKis *vs.* TNFis and JAKis *vs.* non-TNFi bDMARDs groups. Logistic regression adjusted for age, sex, disease duration, and prior exposure to ts/bDMARDs was used to estimate propensity scores. A 1:1 nearest-neighbor matching without replacement method was applied.
Crude change contrast values are presented with 95% confidence intervals.
NRS, numerical rating scale; PS, propensity score; TNFis, tumor necrosis factor inhibitors; JAKis, janus kinase inhibitors; ts/bDMARDs, targeted synthetic/biologic disease-modifying antirheumatic drugs.

bDMARDs = 272, JAKis = 100]) patients. Subgroup analyses stratified according to prior ts/bDMARD exposure status were also performed to partially address potential confounding factors related to treatment history and indication bias. Among ts/bDMARD-naïve patients, the TNFis group showed significantly smaller reductions in pain NRS than the JAKis group after multivariable adjustment (adjusted mean difference: -0.49, 95% CI: -0.85 to -0.13). Similar trends were observed among ts/bDMARD-experienced patients (adjusted mean difference: -0.71, 95% CI: -1.40 to -0.02) (Supplementary Tables 2 and 3). PS matching (JAKis *vs.* TNFis and JAKis *vs.* non-TNFi bDMARDs) was performed. The covariate balance before and after matching was assessed using SMDs, and the results were visualized using a Love plot. After matching, all covariates demonstrated adequate balance (SMD < 0.1). Additionally, the PS distributions before and after matching were plotted to evaluate the overlap between groups. The matched samples showed markedly improved overlap, supporting the appropriateness of the PS model (Supplementary Fig. 2). In PS-matching data, the TNFis group consistently showed less improvement in pain NRS than the JAKis group (crude mean difference: -0.67, 95% CI: -1.03 to -0.30, Table 3). Among individual JAKi, the degree of reduction in pain NRS was comparable between tofacitinib, baricitinib, and upadacitinib users (3.0 ± 2.5 *vs.* 2.8 ± 2.7 *vs.* 2.7 ± 2.3, respectively; $p = 0.636$).

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Pairwise p values: JAKi vs. TNFi (p < 0.0001), JAKi vs. non-TNFi bDMARD (p < 0.0001), TNFi vs. non-TNFi bDMARD (p = 0.1536)

Figure 2. Proportion of patients with rheumatoid arthritis who achieved a pain NRS < 2 while maintaining initial therapy at the 1-year follow-up. The bar graph shows the percentage of patients in all treatment groups who were still using the initial drug while reporting a pain NRS < 2. Group differences were assessed using the chi-square test ($p < 0.0001$). Pairwise comparisons were conducted using two-proportion z-tests, with the following results: JAKis *vs.* TNFis ($p < 0.0001$), JAKis *vs.* non-TNFi bDMARDs ($p < 0.0001$), TNFis *vs.* non-TNFi bDMARDs ($p = 0.1536$). NRS, numerical rating scale; TNFis, tumor necrosis factor inhibitors; JAKis, janus kinase inhibitors; bDMARDs, biologic disease-modifying antirheumatic drugs.

These findings suggest that JAKis are associated with greater pain reduction than TNFis among patients who continued treatment until the first follow-up.

Achievement of a pain NRS < 2 while maintaining the initial drug at 1-year follow-up

The proportion of patients with RA who achieved a pain NRS score < 2 while still using the initial ts/bDMARDs at the 1-year follow-up was 47.4% in the JAKis group, 29.4% in the TNFis group, and 32.4% in the non-TNFi bDMARDs group (Fig. 2). The percentage of patients who achieved a pain NRS score < 2 in the JAKis group was significantly higher than that in the TNFis and non-TNFi bDMARDs groups ($p < 0.001$ for both comparisons). To further evaluate potential differences between responders and non-responders, baseline characteristics were compared according to the achievement of a pain NRS score < 2 at the 1-year follow-up (Supplementary Table 4). Patients who achieved a pain NRS score < 2 were younger, had shorter disease duration, were more likely to be ts/bDMARD-naïve, and had lower baseline disease activity and pain-related measures, including DAS28, SDAI, CDAI, RAPID3, and baseline pain NRS scores, than those who did not achieve a pain NRS score < 2. Multivariable logistic regression analysis conducted using factors with a p value ≤ 0.05 on univariate analysis (Fig. 3) revealed that both the TNFis (OR: 0.515, 95% CI: 0.406–0.652) and non-TNFi bDMARDs (OR: 0.586, 95% CI: 0.458–0.751) groups had significantly lower odds of achieving a pain NRS < 2 (while remaining on the initial drug) than the JAKis group. Other independently associated factors included age (OR: 0.989 per year, 95% CI: 0.983–0.996), follow-up duration (OR: 1.024 per month, 95% CI: 1.012–1.036), and previous treatment history with ts/bDMARDs (OR: 0.723, 95% CI: 0.582–0.897). The results of the univariate logistic regression analysis are presented in Supplementary Table 5.

DISCUSSION

In the present study, among patients who maintained therapy until the first follow-up visit, those treated with JAKis showed greater reductions in pain than those treated with TNFis. Achieving a pain NRS score of < 2 after 1 year of treatment while retaining the initial therapy was more likely

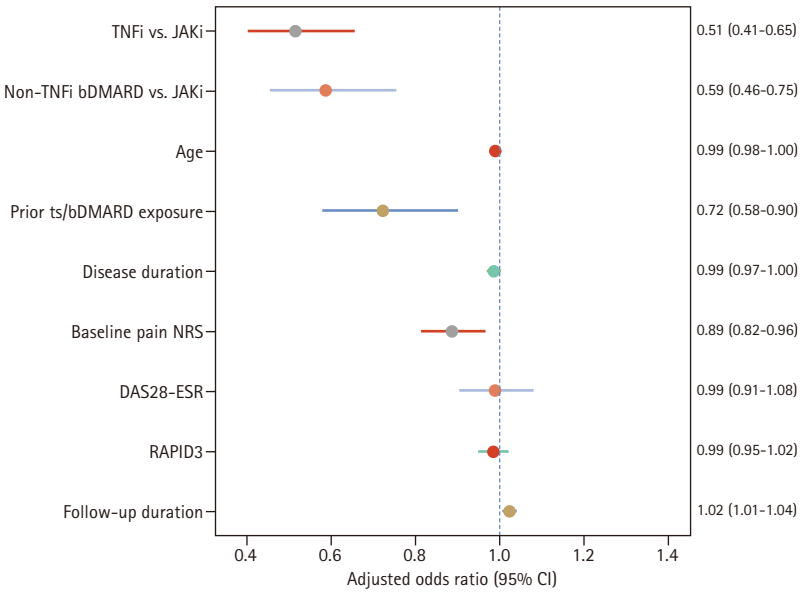


Figure 3. Forest plot of adjusted odds ratios for achieving a pain NRS < 2 while retaining the initial drug at the 1-year follow-up. NRS, numerical rating scale; TNFis, tumor necrosis factor inhibitors; JAKis, janus kinase inhibitors; ts/bDMARDs, targeted synthetic/biologic disease-modifying antirheumatic drugs; DAS28, disease activity score 28 joints; ESR, erythrocyte sedimentation rate; RAPID3, routine assessment of patient index data 3; CI, confidence interval.

among patients receiving JAKis than among those receiving TNFis or non-TNFi bDMARDs. Importantly, subgroup analyses according to prior ts/bDMARD exposure status showed consistent findings favoring JAKis over TNFis in both naïve and experienced populations, suggesting that the observed association was not solely driven by prior biological exposure history.

Two previous studies have shown that JAKis provide greater pain reduction than bDMARDs in patients with RA [15,24]. A post hoc analysis of the RA-BEAM study showed that the proportion of patients with RA reporting 50% and 70% pain reduction at weeks 12 and 24, respectively, was significantly higher in those taking baricitinib than in those taking a TNFi (adalimumab) [24]. A retrospective observational study using Swedish national registry data showed that the JAKis group demonstrated a higher pain reduction effect than the TNFis or rituximab groups at the 3-month follow-up, and a higher proportion of the JAKis group had a lower pain NRS score than the TNFis or tocilizumab groups at the 12-month follow-up [15]. The results of these studies are consistent with those of the present study, suggesting that JAKis may be associated with greater pain reduction than bDMARDs. However, an observational study from the United States comparing third- or fourth-line tofacitinib therapy with third- or fourth-line TNFis combination therapy found no significant difference in pain reduction between the two groups at 6 months [25]. The aforementioned study included only tofacitinib (pan-JAKi) in the JAKi group [25]. In addition, this study did not compare changes in pain NRS scores from baseline [25]. Several JAKis, including tofacitinib, baricitinib, upadacitinib, and filgotinib, have been approved for the treatment of RA. Each has different binding affinities and suppressive effects on different JAK subtypes (JAK1, 2, and 3, and tyrosine kinase 2). Tofacitinib is a pan-JAKi, whereas baricitinib mainly suppresses JAK1 and JAK2; upadacitinib and filgotinib are selective JAK1 inhibitors [26]. The JAK–STAT pathway elicits different cellular responses depending on the binding cytokine(s) and the combination of JAK dimers and STAT subtypes [27]. Therefore, the therapeutic effects and adverse events associated with each JAKi may differ depending on binding affinity for JAK subtypes. ORAL surveillance revealed, for the first time, a link between tofacitinib and an increased risk of cardiovascular disease (CVD) and malignancy [28]; however, many observational studies have reported contradictory results showing that the risk of CVD and malignancy is comparable between JAKis, bDMARDs, and csDMARDs [29-36]. In addition, a network meta-analysis showed that only tofacitinib was associated with an increased risk of CVD compared with TNFis, and that other JAKis have a safety profile comparable to that

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of TNFis [37]. Although head-to-head clinical trials that directly compare the therapeutic effects and adverse events of individual JAKis have not yet been conducted, each JAKi may have a distinct safety profile and therapeutic potential for pain reduction. The present study included three JAKis (tofacitinib, baricitinib, and upadacitinib), and the degree of pain reduction was comparable among the individual JAKis. Further head-to-head studies comparing the therapeutic effects, including the degree of pain reduction, of JAKis should be conducted to better understand these differences.

The pain mechanism in RA is complex, and all three subtypes of pain (nociceptive, neuropathic, and nociplastic) and psychosocial factors can cause pain in patients with RA [12,38]. Chronically elevated levels of pro-inflammatory cytokines have a direct effect on nociceptive pain, and conditions related to joint destruction (e.g., such as carpal tunnel syndrome) can induce neuropathic pain [12]. In addition, increased levels of pro-inflammatory cytokines and subsequent activation of the JAK-STAT pathway may induce immune-mediated pain pathways that modulate peripheral and central sensitization [39]. For example, *in vitro* studies suggest that granulocyte–macrophage colony-stimulating factor, interleukin (IL)-6, IL-17, and interferon-γ increase pain susceptibility in the dorsal root ganglion, and affect neural cell activation and survival [39]. Therefore, pain mechanisms in RA may be affected by various cytokines and JAK-STAT pathway [12]. The selectivity of JAKis for JAK subtypes can differ; however, JAKis typically suppress multiple cytokine signals, differentiating them from bDMARDs [40]. This may explain the better pain reduction effects of JAKis; however, further studies investigating the *in vivo* interactions between JAKis and pain-related cell signals are needed.

The present study has several limitations. First, the KOBIO registry is an observational cohort, and results from observational studies have inherent limitations compared with those from randomized controlled trials. The duration between baseline and first follow-up in the present study was heterogeneous owing to the characteristics of the study design. Second, the groups were heterogeneous with respect to age, disease duration, and prior exposure to ts/bDMARDs, all of which could have affected the primary outcome (degree of pain reduction). We performed subgroup and PS-matching analyses to overcome this limitation; however, we did not completely overcome it. Third, there were substantial differences in the number of patients enrolled in each group. In particular, the number of rituximab users was very low. Therefore, we merged rituximab, abatacept, and tocilizumab into one group, the non-TNFi bDMARDs group; however, non-TNFi bDMARDs have different mechanisms of action and may differ in efficacy with respect to pain reduction. Fourth, the present analysis may have been affected by responder-retention bias because patients who discontinued therapy before the first follow-up owing to inefficacy or adverse events were less likely to contribute to follow-up pain assessments. Therefore, the findings should not be interpreted as strict intention-to-treat comparisons of treatment effectiveness. Rather, the results reflected pain outcomes among patients who received therapy and underwent follow-up assessments in routine clinical practice. Fifth, although multivariate adjustment and PS matching were performed, residual confounding factors related to treatment indication, physician preference, disease severity, comorbid pain conditions, and prior treatment history may still exist. Patients who achieved a low pain status at follow-up demonstrated a lower baseline disease burden and more favorable clinical characteristics than non-responders, suggesting that baseline patient characteristics may have influenced subsequent pain outcomes despite multivariable adjustment. Furthermore, because the outcome assessment depended on treatment retention and the availability of follow-up data, the present findings should be interpreted within the context of a treatment retention-based observational analysis. Therefore, the observed associations may reflect both treatment effectiveness and factors related to treatment persistence in routine clinical practice.

In conclusion, among patients who continued treatment until follow-up, JAKis were associated with greater pain reduction than TNFis. However, these findings should be interpreted within the context of a treatment-retention-based observational analysis and should not be regarded as definitive evidence of comparative efficacy. Further prospective comparative studies are required to confirm these findings.

KEY MESSAGE

1. Persistent pain remains an important unmet need for patients with RA, even among those achieving inflammatory disease control.
2. In this real-world observational cohort, JAKis were associated with greater pain reduction than TNFis in patients who remained on therapy until follow-up.
3. Further prospective studies are needed to determine whether JAKis are associated with greater pain reduction than other bDMARDs.

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Correspondence to
Hong Ki Min, M.D., Ph.D.
Division of Rheumatology, Department of Internal Medicine, Research Institute of Medical Science, Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05029, Korea
Tel: +82-2-2030-6741
E-mail: alsghdrl1921@naver.com
https://orcid.org/0000-0003-1147-1046

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CRedit authorship contributions
Howook Jeon: investigation, data curation, formal analysis; Hong Ki Min: conceptualization, methodology, investigation, data curation,

formal analysis, validation, software, writing - original draft, writing - review & editing, visualization, project administration

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Supplementary Table 1. Pairwise post-hoc comparisons for baseline characteristics among treatment groups

Variable	Group 1	Group 2	Adjusted *p* value
Age	JAKi	TNFi	0.002
Age	JAKi	Non-TNFi bDMARD	0.602
Age	TNFi	Non-TNFi bDMARD	< 0.001
Disease duration	JAKi	TNFi	0.026
Disease duration	JAKi	Non-TNFi bDMARD	0.977
Disease duration	TNFi	Non-TNFi bDMARD	0.008
Swollen joint count	JAKi	TNFi	< 0.001
Swollen joint count	JAKi	Non-TNFi bDMARD	< 0.001
Swollen joint count	TNFi	Non-TNFi bDMARD	0.121
Tender joint count	JAKi	TNFi	< 0.001
Tender joint count	JAKi	Non-TNFi bDMARD	< 0.001
Tender joint count	TNFi	Non-TNFi bDMARD	0.202
Patient's global assessment	JAKi	TNFi	0.001
Patient's global assessment	JAKi	Non-TNFi bDMARD	< 0.001
Patient's global assessment	TNFi	Non-TNFi bDMARD	0.003
Physician's global assessment	JAKi	TNFi	0.126
Physician's global assessment	JAKi	Non-TNFi bDMARD	0.013
Physician's global assessment	TNFi	Non-TNFi bDMARD	0.406
ESR	JAKi	TNFi	0.628
ESR	JAKi	Non-TNFi bDMARD	0.004
ESR	TNFi	Non-TNFi bDMARD	0.007
DAS28-ESR	JAKi	TNFi	< 0.001
DAS28-ESR	JAKi	Non-TNFi bDMARD	< 0.001
DAS28-ESR	TNFi	Non-TNFi bDMARD	0.041
DAS28-CRP	JAKi	TNFi	< 0.001
DAS28-CRP	JAKi	Non-TNFi bDMARD	< 0.001
DAS28-CRP	TNFi	Non-TNFi bDMARD	0.127
SDAI	JAKi	TNFi	< 0.001
SDAI	JAKi	Non-TNFi bDMARD	< 0.001
SDAI	TNFi	Non-TNFi bDMARD	0.454
CDAI	JAKi	TNFi	< 0.001
CDAI	JAKi	Non-TNFi bDMARD	< 0.001
CDAI	TNFi	Non-TNFi bDMARD	0.777
Pain NRS	JAKi	TNFi	0.009
Pain NRS	JAKi	Non-TNFi bDMARD	< 0.001
Pain NRS	TNFi	Non-TNFi bDMARD	0.255
RAPID-3	JAKi	TNFi	0.008
RAPID-3	JAKi	Non-TNFi bDMARD	< 0.001
RAPID-3	TNFi	Non-TNFi bDMARD	0.010
ts/bDMARD-naïve	TNFi	Non-TNFi bDMARD	< 0.001
ts/bDMARD-naïve	TNFi	JAKi	0.001
ts/bDMARD-naïve	Non-TNFi bDMARD	JAKi	0.002

Supplementary Table 1. Continued

Variable	Group 1	Group 2	Adjusted *p* value
Dyslipidemia	TNFi	Non-TNFi bDMARD	0.009
Dyslipidemia	TNFi	JAKi	0.035
Dyslipidemia	Non-TNFi bDMARD	JAKi	1.000
Osteoporosis	TNFi	Non-TNFi bDMARD	< 0.001
Osteoporosis	TNFi	JAKi	0.204
Osteoporosis	Non-TNFi bDMARD	JAKi	< 0.001

JAKis, janus kinase inhibitors; TNFis, tumor necrosis factor inhibitors; ts/bDMARDs, targeted synthetic/biologic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; DAS28, disease activity score 28 joints; SDAI, simplified disease activity index; CDAI, clinical disease activity index; NRS, numeric rating scale; RAPID3, routine assessment of patient index data 3.

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Supplementary Table 2. Subgroup analysis comparing ts/bDMARD-naïve RA patients with other groups to assess baseline pain NRS scores and mean changes at first follow-up

ts/bDMARD-naïve	N	Baseline mean pain NRS (0–10)	Mean change of pain NRS (baseline – first f/u)	Crude change contrast	Adjusted change contrast
TNFis	960	6.18 ± 2.15	2.36 ± 2.89	-0.49 (-0.85 to -0.13)	-0.49 (-0.85 to -0.13)
Non-TNFi bDMARDs	573	6.25 ± 2.15	2.77 ± 2.91	-0.08 (-0.47 to 0.31)	-0.08 (-0.47 to 0.31)
JAKis	322	5.71 ± 2.25	2.85 ± 2.56	Ref	Ref

Values are presented as the mean ± standard deviation.
Differences in the mean change in the pain NRS were evaluated using linear regression. Crude and adjusted change contrasts (with 95% confidence intervals) are shown for each group (compared with the JAKis reference group). Adjusted estimates were derived from multivariable models controlled for age, sex, and disease duration.
Negative values indicate less improvement in the pain NRS (compared with the JAKis group).
RA, rheumatoid arthritis; NRS, numeric rating scale; TNFis, tumor necrosis factor inhibitors; JAKis, janus kinase inhibitors; ts/bDMARDs, targeted synthetic/biologic disease-modifying antirheumatic drugs.

Supplementary Table 3. Subgroup analysis to compare ts/bDMARD-experienced RA patients with other subgroups to assess baseline pain NRS score and mean changes at first follow-up

ts/bDMARD-experienced	N	Baseline mean pain NRS (0–10)	Mean change of pain NRS (baseline – first f/u)	Crude change contrast	Adjusted change contrast
TNFis	188	6.11 ± 2.39	2.02 ± 3.07	-0.72 (-1.40 to -0.03)	-0.71 (-1.40 to -0.02)
Non-TNFi bDMARDs	272	6.48 ± 2.30	2.25 ± 2.75	-0.49 (-1.13 to 0.16)	-0.47 (-1.12 to 0.18)
JAKis	100	6.05 ± 2.13	2.74 ± 2.48	Ref	Ref

Values are presented as the mean ± standard deviation.
Differences in the mean change in the pain NRS were evaluated using linear regression. Crude and adjusted change contrasts (with 95% confidence intervals) are shown for each group (compared with the JAKis reference group). Adjusted estimates were derived from multivariable models controlled for age, sex, and disease duration.
Negative values indicate less improvement in the pain NRS (compared with the JAKis group).
RA, rheumatoid arthritis; NRS, numeric rating scale; TNFis, tumor necrosis factor inhibitors; JAKis, janus kinase inhibitors; ts/bDMARDs, targeted synthetic/biologic disease-modifying antirheumatic drugs.

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Supplementary Table 4. Comparison of baseline characteristics between RA patients who achieved pain NRS < 2 or not

Variable	Pain NRS ≥ 2 at 1 year f/u (N = 1,495)	Pain NRS < 2 at 1 year f/u (N = 920)	*p* value
Female	1,253 (83.8)	746 (81.1)	0.096
Age (yr)	55.32 ± 12.79	53.22 ± 12.90	< 0.001
Disease duration (yr)	8.15 ± 7.95	6.96 ± 6.41	< 0.001
BMI (kg/m^2)	22.82 ± 3.44	22.70 ± 3.51	0.422
ts/bDMARD-naïve	1: 1,111 (74.3); 2: 384 (25.7)	1: 744 (80.9); 2: 176 (19.1)	< 0.001
Smoking status			0.845
Ex-smoker	132 (8.8)	82 (8.9)	
Current smoker	127 (8.5)	72 (7.8)	
Never smoker	1,236 (82.7)	766 (83.3)	
Comorbidities			
Diabetes mellitus	180 (12.0)	107 (11.6)	0.812
Hypertension	476 (31.8)	246 (26.7)	0.009
Dyslipidemia	340 (22.7)	197 (21.4)	0.476
Migraine	5 (0.3)	3 (0.3)	1.000
Osteoporosis	403 (27.0)	185 (20.1)	< 0.001
Hyperthyroidism	21 (1.4)	8 (0.9)	0.327
Hypothyroidism	73 (4.9)	52 (5.7)	0.463
CKD	25 (1.7)	11 (1.2)	0.444
MDD	39 (2.6)	14 (1.5)	0.104
Malignancy	3 (0.2)	6 (0.7)	0.154
Swollen joint count (0–44)	6.68 ± 5.49	6.07 ± 4.89	0.005
Tender joint count (0–44)	8.96 ± 7.00	7.54 ± 5.87	< 0.001
Patient's global assessment (0–10)	6.92 ± 1.91	6.40 ± 2.18	< 0.001
Physician's global assessment (0–10)	6.49 ± 1.79	6.30 ± 1.84	0.009
ESR (mm/hr)	49.11 ± 28.28	46.86 ± 27.89	0.056
hs-CRP (mg/dL)	2.16 ± 3.02	2.11 ± 3.40	0.678
DAS28-ESR	5.57 ± 1.14	5.34 ± 1.14	< 0.001
DAS28-CRP	4.85 ± 1.13	4.66 ± 1.12	< 0.001
SDAI	29.19 ± 11.87	26.86 ± 11.19	< 0.001
CDAI	27.04 ± 11.22	24.76 ± 10.14	< 0.001
Pain NRS (0–10)	6.46 ± 2.06	5.66 ± 2.35	< 0.001
RAPID3	15.76 ± 5.34	13.76 ± 5.87	< 0.001
EQ-VAS	5.92 ± 1.91	4.99 ± 2.19	< 0.001
RF positive	1,174 (81.6)	736 (83.6)	0.243
ACPA positive	1,058 (84.8)	680 (87.4)	0.114

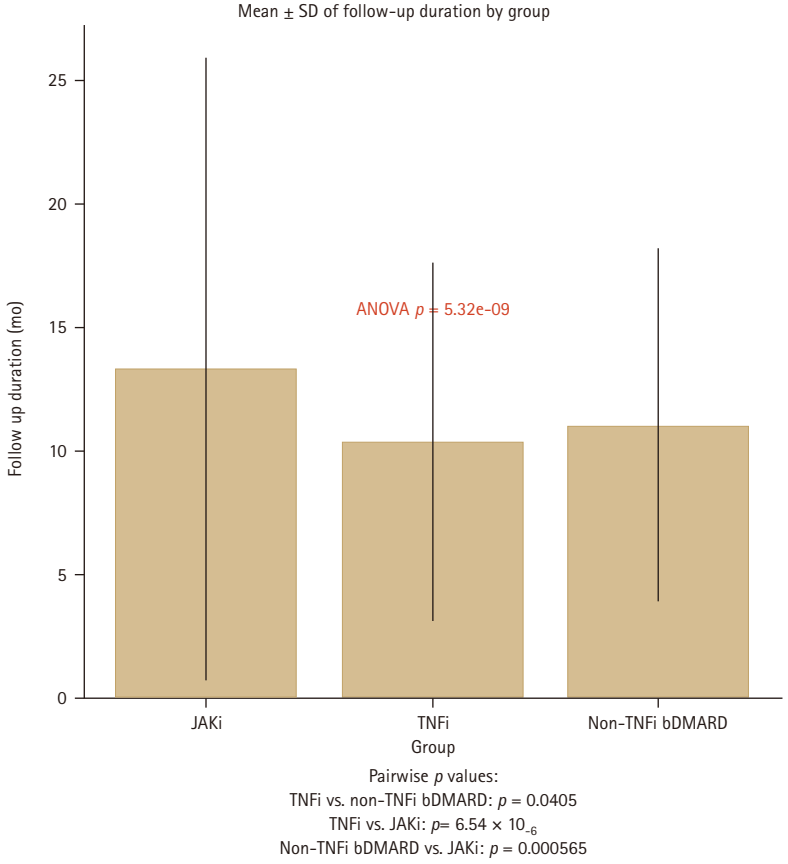
Data are presented as the mean ± standard deviation or as numbers (%).
RA, rheumatoid arthritis; BMI, body mass index; ts/bDMARDs, targeted synthetic/biologic disease-modifying antirheumatic drugs; CKD, chronic kidney disease; MDD, major depressive disorder; ESR, erythrocyte sedimentation rate; hs-CRP, high sensitive C-reactive protein; DAS28, disease activity score 28 joints; SDAI, simplified disease activity index; CDAI, clinical disease activity index; NRS, numeric rating scale; RAPID3, routine assessment of patient index data 3; EQ-VAS, EuroQol-visual analogue scale; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody.

Supplementary Table 5. Univariate logistic regression analysis of factors associated with achievement of a pain NRS < 2 while maintaining the initial drug at the 1-year follow-up

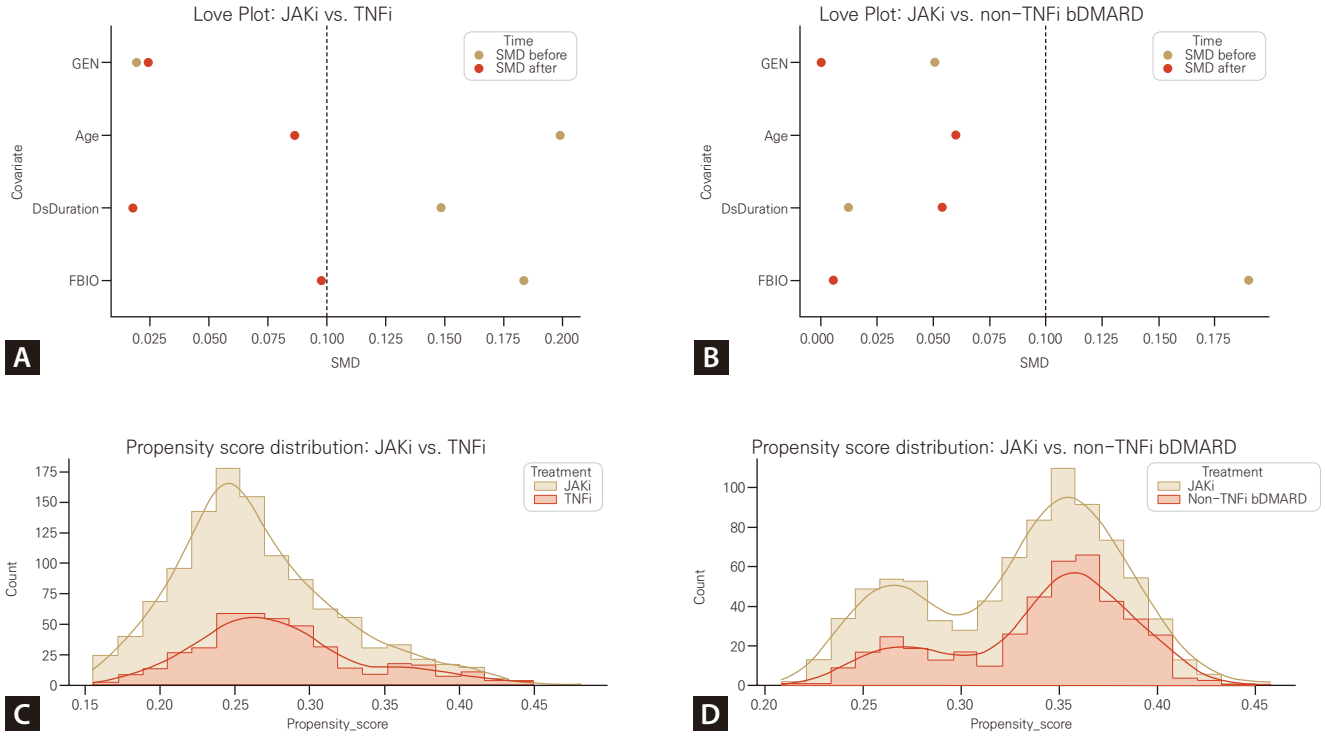
Variable	Odds ratio	95% confidence interval	*p* value
Age (yr)	0.987	0.980–0.994	0.0005
Female	0.970	0.762–1.235	0.8053
BMI (kg/m^2)	0.984	0.958–1.011	0.2405
Disease duration (yr)	0.984	0.971–0.997	0.0168
Follow-up duration (mo)	1.027	1.016–1.039	< 0.0001
Baseline pain NRS (0–10)	0.889	0.853–0.927	< 0.0001
ESR (mm/hr)	0.997	0.993–1.000	0.0502
hs-CRP (mg/dL)	1.005	0.977–1.034	0.7267
RF positive	0.888	0.694–1.135	0.3420
ACPA positive	0.852	0.650–1.116	0.2445
DAS28-ESR	0.877	0.808–0.951	0.0016
RAPID3	0.955	0.939–0.971	< 0.0001
Smoking status			
Non-smoker	Ref		
Ex-smoker	0.775	0.551–1.091	0.1444
Current smoker	0.779	0.552–1.100	0.1562
ts/bDMARD-experienced	0.701	0.554–0.887	0.0031
JAKis	Ref		
TNFis	0.454	0.353–0.583	< 0.0001
Non-TNFi bDMARDs	0.536	0.414–0.696	< 0.0001

JAKis, janus kinase inhibitors; TNFis, tumor necrosis factor inhibitors; BMI, body mass index; ts/bDMARDs, targeted synthetic/biologic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; hs-CRP, highly sensitive C-reactive protein; DAS28, disease activity score 28 joints; NRS, numeric rating scale; RAPID3, routine assessment of patient index data 3; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies.

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Supplementary Figure 1. Follow-up duration by treatment group. TNFis, tumor necrosis factor inhibitors; JAKis, janus kinase inhibitors; bDMARDs, biologic disease-modifying antirheumatic drugs.



Supplementary Figure 2. Love Plot of covariate balance and the distribution of propensity scores before and after matching. Standardized mean differences (SMDs) for each covariate were plotted before and after propensity score matching to assess the covariate balance between the treatment groups (A) JAKis *vs.* TNFis and (B) JAKis *vs.* non-TNFi bDMARDs. An absolute SMD < 0.1 was considered indicative of an acceptable balance. Post-matching, all covariates demonstrated an improved balance, confirming the effectiveness of the matching process. The distribution of estimated propensity scores is shown for each treatment group before and after 1:1 nearest-neighbor matching for (C) JAKis *vs.* TNFis and (D) JAKis *vs.* non-TNFi bDMARDs. Matching resulted in a marked improvement in the overlap of propensity scores between groups, indicating that matched samples were more comparable in terms of observed covariates. TNFis, tumor necrosis factor inhibitors; JAKis, janus kinase inhibitors; bDMARDs, biologic disease-modifying antirheumatic drugs.

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