



Title	Clinical outcomes of molecular-targeted therapies for rheumatoid arthritis: comparison between orthopaedic surgeons and rheumatologists in the multicenter retrospective ANSWER cohort
Author(s)	Etani, Yuki; Okita, Yasutaka; Tsujimoto, Kohei et al.
Citation	Clinical Rheumatology. 2026
Version Type	VoR
URL	<a href="https://hdl.handle.net/11094/104801">https://hdl.handle.net/11094/104801</a>
rights	This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.
Note	

*The University of Osaka Institutional Knowledge Archive : OUKA*

<https://ir.library.osaka-u.ac.jp/>

The University of Osaka



# Clinical outcomes of molecular-targeted therapies for rheumatoid arthritis: comparison between orthopaedic surgeons and rheumatologists in the multicenter retrospective ANSWER cohort

Yuki Etani<sup>1</sup> · Yasutaka Okita<sup>2</sup> · Kohei Tsujimoto<sup>2</sup> · Takaaki Noguchi<sup>3</sup> · Koichi Murata<sup>4,5</sup> · Takayuki Fujii<sup>4,5</sup> · Iku Shirasugi<sup>6</sup> · Mai Yamashita<sup>6</sup> · Koji Nagai<sup>7</sup> · Ayaka Yoshikawa<sup>7</sup> · Motomu Hashimoto<sup>8</sup> · Tadashi Okano<sup>9</sup> · Yuji Nozaki<sup>10</sup> · Tetsu Itami<sup>10</sup> · Yonsu Son<sup>11</sup> · Hidehiko Makino<sup>11</sup> · Wataru Yamamoto<sup>12</sup> · Atsushi Kumanogoh<sup>2</sup> · Seiji Okada<sup>3</sup> · Ken Nakata<sup>13</sup> · Kosuke Ebina<sup>1,3</sup>

Received: 12 February 2026 / Revised: 16 March 2026 / Accepted: 18 March 2026  
© The Author(s) 2026

## Abstract

**Objectives** In Japan, pharmacological treatment for rheumatoid arthritis (RA), including biologic disease-modifying antirheumatic drugs (bDMARDs) and Janus kinase inhibitors (JAKi), is provided by both orthopaedic surgeons and rheumatologists. However, differences in patient characteristics, treatment selection, and outcomes between these two clinical settings have not been fully elucidated. This study aimed to compare these factors using real-world data.

**Methods** Using the ANSWER cohort, we identified 7268 RA treatment courses initiating bDMARDs or JAKi between August 2002 and May 2023. Patients were classified into orthopaedic surgeon–managed and rheumatologist–managed groups. Patient characteristics and treatment patterns were compared. Treatment retention due to ineffectiveness and adverse events was assessed using Cox proportional hazards models to estimate hazard ratios (HRs) adjusted for potential confounders.

**Results** Compared with the rheumatologist–managed group, patients managed by orthopaedic surgeons had longer disease duration, higher seropositivity, greater functional impairment, although lower comorbidity prevalence such as hypertension, dyslipidemia, and diabetes mellitus. Methotrexate, tumor necrosis factor inhibitors, JAKi, and intra-articular injections were used more frequently, whereas oral glucocorticoids were used less frequently. After adjustment, treatment retention due to ineffectiveness was comparable between groups (HR 0.98, 95% CI 0.83–1.17), and changes in disease activity were similar. Discontinuation due to adverse events was significantly less frequent in the orthopaedic surgeon–managed group (HR 0.61, 95% CI 0.46–0.82).

**Conclusions** Despite differences in patient profiles and treatment patterns, molecular-targeted therapy managed by orthopaedic surgeons achieved comparable effectiveness and was associated with a lower risk of discontinuation due to adverse events compared with rheumatology care.

## Key Points

- Patients managed by orthopaedic surgeons had longer disease duration, higher seropositivity, and more advanced structural and functional impairment than those managed by rheumatologists.
- Despite these differences, treatment effectiveness and disease activity improvement with bDMARDs or JAK inhibitors were comparable between specialties after adjustment for confounders.
- Treatment discontinuation due to adverse events was less frequent in patients managed by orthopaedic surgeons.
- Guideline-based management may enable consistent clinical outcomes across different specialties in real-world rheumatoid arthritis care.

**Keywords** bDMARDs · Drug retention · Janus kinase inhibitors · Real-world data · Rheumatoid arthritis

## Introduction

Biologic disease-modifying antirheumatic drugs (bDMARDs), including tumor necrosis factor inhibitors (TNFi), anti-interleukin-6 receptor antibodies (aIL-6Ra), and cytotoxic

Extended author information available on the last page of the article

T-lymphocyte antigen 4-immunoglobulin fusion protein (CTLA4-Ig), and Janus kinase inhibitors (JAKi) have substantially improved disease control and long-term outcomes in patients with rheumatoid arthritis (RA) [1–3]. Current treatment strategies emphasize early intervention and tight disease activity control based on established clinical guidelines [3, 4]. In routine clinical practice, however, the organization of RA care differs across countries. Japan represents a unique clinical setting in which both rheumatology-oriented orthopaedic surgeons and rheumatologists routinely provide pharmacological treatment for RA, including bDMARDs and JAKi [5, 6]. This dual-care system is uncommon worldwide, where pharmacological management of RA is generally centralized within rheumatology. In daily clinical practice in Japan, patients and physicians from other specialties frequently question whether advanced pharmacological therapy for RA should be managed in orthopaedic surgery clinics or rheumatology clinics, with a common perception that rheumatology clinics may be more experienced in pharmacological management and therefore associated with fewer treatment discontinuations due to ineffectiveness or adverse events.

Previous analyses from the IORRA cohort have reported differences in patient characteristics and changes in disease activity between patients managed in orthopaedic surgery and rheumatology clinics in Japan [5]. However, studies that account for differences in patient backgrounds through statistical adjustment and compare treatment retention between these two clinical settings are still lacking. Drug retention is considered a reliable measure of a drug's safety, efficacy, and tolerability, despite the potential influence of diverse factors, such as variations in healthcare provision and patient demographics [7].

We therefore hypothesized that patient characteristics, treatment patterns, and treatment outcomes may differ between RA patients treated with bDMARDs or JAKi in orthopaedic surgery clinics and those treated in rheumatology clinics. Using data from the Kansai Consortium for Well-being of Rheumatic Disease Patients (ANSWER) cohort, the primary endpoint of this study was to compare treatment retention between the two clinical settings according to reasons for treatment discontinuation. Secondary endpoints included comparisons of baseline patient characteristics and treatment-related variables.

## Materials and methods

### Patients

The ANSWER cohort is a multicenter, observational registry of patients with rheumatic diseases in the Kansai region in Japan [8–11]. We retrospectively collected patient data from eight major university-affiliated hospitals and

one large community hospital: Osaka University, Kyoto University, Osaka Metropolitan University, Osaka Medical and Pharmaceutical University, Kansai Medical University, Kobe University, Nara Medical University, Kinki University, and Osaka Red Cross Hospital. Pharmacological treatment was provided by rheumatologists or rheumatology-oriented orthopaedic surgeons. All treating physicians, including orthopaedic surgeons, were board-certified rheumatology specialists certified by the Japan College of Rheumatology (JCR). Subsequently, a retrospective medical chart review was conducted to determine whether bDMARDs or JAKi were prescribed by orthopaedic surgeons or rheumatologists, and patients were classified into the orthopaedic surgeon group or the rheumatologist group accordingly. RA diagnosis was based on the 1987 American College of Rheumatology (ACR) [12] or the 2010 ACR/European League Against Rheumatism (EULAR) RA classification criteria [13]. Treatment with bDMARDs and JAKi was at the discretion of the treating physician, based on the JCR guidelines [4]. The 2024 JCR guidelines recommend escalating therapy with additional conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or moving to phase II treatment with bDMARDs or JAKi for patients not achieving low disease activity on initial csDMARDs therapy (mainly by methotrexate [MTX]). Drug dosages were prescribed according to the manufacturers' recommendations.

We included patients treated with bDMARDs or JAKi from August 2002 to May 2023, with complete records of treatment start and end dates and reasons for discontinuation. We categorized the reasons for discontinuation into four main categories: (1) ineffectiveness (including both primary and secondary failures), (2) toxic adverse events (including infections, dermatologic, pulmonary, cardiovascular, hematologic, and malignant complications), (3) non-toxic reasons (patient preference, desire for pregnancy, etc.), and (4) remission [14]. We excluded those with missing essential data, such as age, sex, or disease duration. We also collected information on concomitant medications, including dosages of MTX, glucocorticoids (GCs; prednisolone [PSL] equivalent), and other csDMARDs, as well as clinical and laboratory variables, including disease activity scores such as the Clinical Disease Activity Index (CDAI) and Disease Activity Score in 28 joints using the C-reactive protein (DAS28-CRP) and erythrocyte sedimentation rate (DAS28-ESR), serological status for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA), estimated glomerular filtration rate (eGFR), and Krebs von den Lungen-6 (KL-6).

### Statistical analysis

To compare baseline patient characteristics and treatment-related variables, continuous variables were analyzed using the Mann–Whitney *U* test, whereas

categorical variables were compared using the chi-square test. To compare treatment retention between the two groups, Kaplan–Meier curves were generated and adjusted Cox proportional hazards regression analyses were performed to estimate hazard ratios (HRs). These analyses were adjusted for previously identified potential confounders, including baseline age, sex, disease duration, body mass index, RF positivity, ACPA positivity, eGFR, KL-6, comorbid hypertension, dyslipidemia, and diabetes mellitus, concomitant MTX use, concomitant GC use and other csDMARDs use, initiated drug class (TNFi, aIL-6Ra, CTLA4-Ig, or JAKi), bDMARDs or JAKi-naïve status, and Steinbrocker stage and functional class [15–18]. To compare disease activity control after initiation of bDMARDs or JAKi, mean CDAI values at baseline and at 1, 3, 6, and 12 months after treatment initiation were compared between the two groups using the Mann–Whitney *U* test at each time point. In addition, chi-square tests were used to compare CDAI remission rates between the two groups at each time point. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (R Foundation for Statistical Computing, Vienna, Austria) [19]. Statistical significance was considered at  $P < 0.05$  in a two-sided test.

## Results

### Baseline characteristics

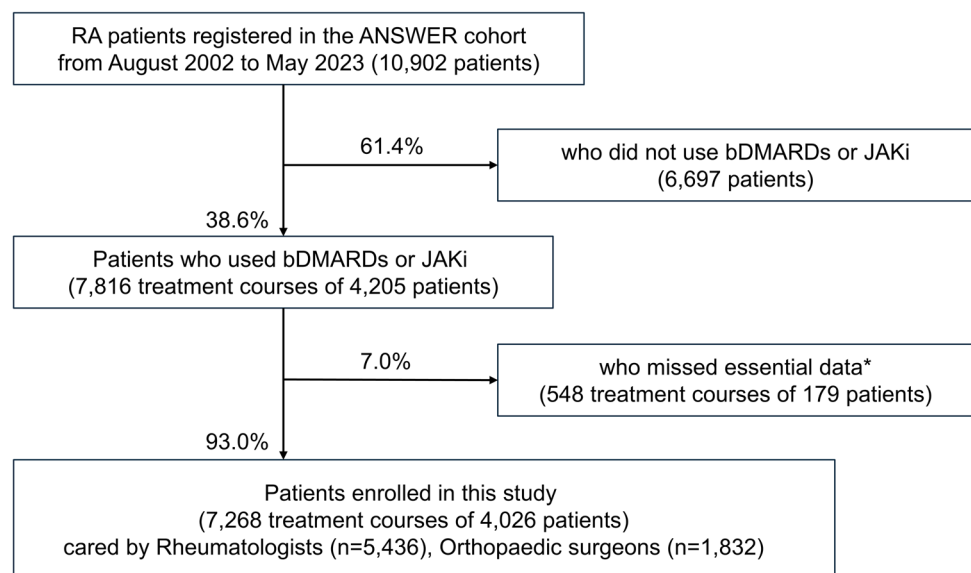
The patient selection process is shown in Fig. 1. A total of 7268 treatment courses from 4026 patients with RA were

included, comprising 5436 treatment courses managed by rheumatologists and 1832 treatment courses managed by orthopaedic surgeons. Baseline characteristics at treatment initiation are summarized in Table 1. Patients managed by orthopaedic surgeons had a longer disease duration and higher positivity rates for RF and ACPA than those managed by rheumatologists. More advanced functional impairment and structural joint damage were observed in the orthopaedic surgeon group, as indicated by higher Health Assessment Questionnaire Disability Index (HAQ-DI) scores and more advanced Steinbrocker stage and functional class. Patients in the rheumatologist group showed a higher prevalence of hypertension, dyslipidemia, and diabetes mellitus, along with lower baseline eGFR and higher KL-6 levels.

### Treatment characteristics

Treatment-related characteristics at treatment initiation are summarized in Table 2. Supplementary Table 1 presents the distribution of individual bDMARDs and JAKi prescribed in this study. The distribution of initiated drug classes differed between the two groups. TNFi and JAKi were more frequently prescribed by orthopaedic surgeons, whereas aIL-6Ra and CTLA4-Ig were more commonly prescribed by rheumatologists. MTX was used more frequently in the orthopaedic surgeon group; however, the prescribed dose was lower compared with the rheumatologist group. Concomitant use of other csDMARDs was less frequent among patients managed by orthopaedic surgeons. Regarding GCs use, oral GCs were used less frequently in the orthopaedic surgeon group, whereas intra-articular GCs injections during follow-up were more common.

**Fig. 1** Flowchart of the patients' enrollment. Flow diagram illustrating patient selection from the ANSWER cohort database. Abbreviations: bDMARDs, biological disease-modifying anti-rheumatic drugs; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis



**Table 1** Baseline characteristics of patients at initiation of bDMARD or JAK inhibitor therapy

Variable	Rheumatologists ( <i>n</i> =5436)	Orthopaedic surgeons ( <i>n</i> =1832)	<i>P</i> value
Age (years)	60.4 ± 15.3	60.1 ± 14.5	0.509
Female sex (%)	82.2	86.0	<0.001
Disease duration (years)	9.1 ± 9.4	13.7 ± 12.1	<0.001
BMI (kg/m <sup>2</sup> )	22.1 ± 3.7	22.2 ± 3.8	0.436
RF positivity (%)	76.4	81.4	<0.001
ACPA positivity (%)	79.4	85.1	<0.001
CRP (mg/dL)	1.6 ± 2.6	1.5 ± 2.4	0.316
ESR (mm/h)	36.2 ± 28.4	40.4 ± 29.1	<0.001
eGFR (mL/min/1.73 m <sup>2</sup> )	75.7 ± 23.9	78.1 ± 25.6	0.006
KL-6 (U/mL)	315.6 ± 326.9	285.7 ± 187.1	<0.001
TJC (28 joints)	4.0 ± 4.8	4.1 ± 5.1	0.900
SJC (28 joints)	3.7 ± 4.3	3.7 ± 4.1	0.770
Patient VAS (mm)	49.3 ± 26.9	48.2 ± 28.0	0.299
Physician VAS (mm)	38.4 ± 24.7	37.2 ± 24.1	0.252
DAS28-CRP	3.7 ± 1.3	3.6 ± 1.3	0.515
DAS28-ESR	4.3 ± 1.4	4.4 ± 1.4	0.156
CDAI	16.6 ± 10.9	16.3 ± 10.7	0.528
SDAI	18.3 ± 12.0	17.8 ± 11.6	0.342
HAQ-DI	1.0 ± 0.8	1.1 ± 0.9	0.020
bDMARDs or JAKi naive (%)	52.4	48.9	0.009
2nd bDMARDs or JAKi (%)	23.5	25.9	0.034
≥3rd bDMARDs or JAKi (%)	24.1	25.2	0.367
Comorbid hypertension (%)	13.7	8.4	<0.001
Comorbid dyslipidemia (%)	11.2	3.7	<0.001
Comorbid diabetes mellitus (%)	15.8	8.1	<0.001
Steinbrocker classification			
Class I (%)	31.6	29.5	0.159
Class II (%)	48.0	42.3	<0.001
Class III (%)	17.9	24.9	<0.001
Class IV (%)	2.5	3.3	0.125
Stage I (%)	35.2	16.2	<0.001
Stage II (%)	27.1	16.9	<0.001
Stage III (%)	13.6	28.4	<0.001
Stage IV (%)	24.0	38.5	<0.001

Values are presented as mean ± standard deviation or percentage. Differences between groups were assessed using the Mann–Whitney *U* test for continuous variables and the chi-square test for categorical variables

**Abbreviations:** ACPA anti-cyclic citrullinated peptide antibody, bDMARDs biologic disease-modifying antirheumatic drugs, BMI body mass index, CDAI Clinical Disease Activity Index, CRP C-reactive protein, DAS28 Disease Activity Score in 28 joints, eGFR estimated glomerular filtration rate, ESR erythrocyte sedimentation rate, HAQ-DI Health Assessment Questionnaire Disability Index, JAKi Janus kinase inhibitor, KL-6 Krebs von den Lungen-6, RF rheumatoid factor, SDAI Simplified Disease Activity Index, SJC swollen joint count, TJC tender joint count, VAS visual analog scale

## Comparison of treatment retention (adjusted Cox proportional hazards analysis)

Kaplan–Meier curves for treatment discontinuation due to ineffectiveness and adverse events are shown in Fig. 2, and the results of adjusted Cox proportional hazards regression analyses are summarized in Table 3. After adjustment for baseline patient characteristics and treatment-related variables, the adjusted HR for treatment discontinuation due to ineffectiveness in the orthopaedic surgeon group was not significantly different from that in the rheumatologist group (HR 0.98, 95% CI 0.83–1.17). In contrast, treatment discontinuation due to adverse events was less frequent among patients managed by orthopaedic surgeons (HR 0.61, 95% CI 0.46–0.82). Supplementary Tables 2 and 3 present the HRs for individual risk factors associated with treatment discontinuation due to ineffectiveness and adverse events, respectively. For discontinuation due to ineffectiveness, dyslipidemia, concomitant GC use, and prior exposure to bDMARDs or JAKi were identified as significant risk factors. In contrast, for discontinuation due to adverse events, male sex, comorbid hypertension, and concomitant GC use were associated with an increased risk. Notably, even after adjustment for these factors, management by orthopaedic surgeons remained independently associated with a lower risk of treatment discontinuation due to adverse events. Regarding remission, treatment discontinuation after achieving remission tended to be more frequent among patients managed by rheumatologists than among those managed by orthopaedic surgeons.

## Changes in disease activity after bDMARD or JAKi initiation

Changes in disease activity after initiation of bDMARDs or JAKi are shown in Fig. 3a. Mean Clinical Disease Activity Index (CDAI) values improved over time in both groups. At baseline and at 1, 3, 6, and 12 months after treatment initiation, no significant differences in mean CDAI values were observed between patients managed by orthopaedic surgeons and those managed by rheumatologists. In addition, CDAI remission rates at each time point did not differ significantly between the two groups (Fig. 3b).

## Discussion

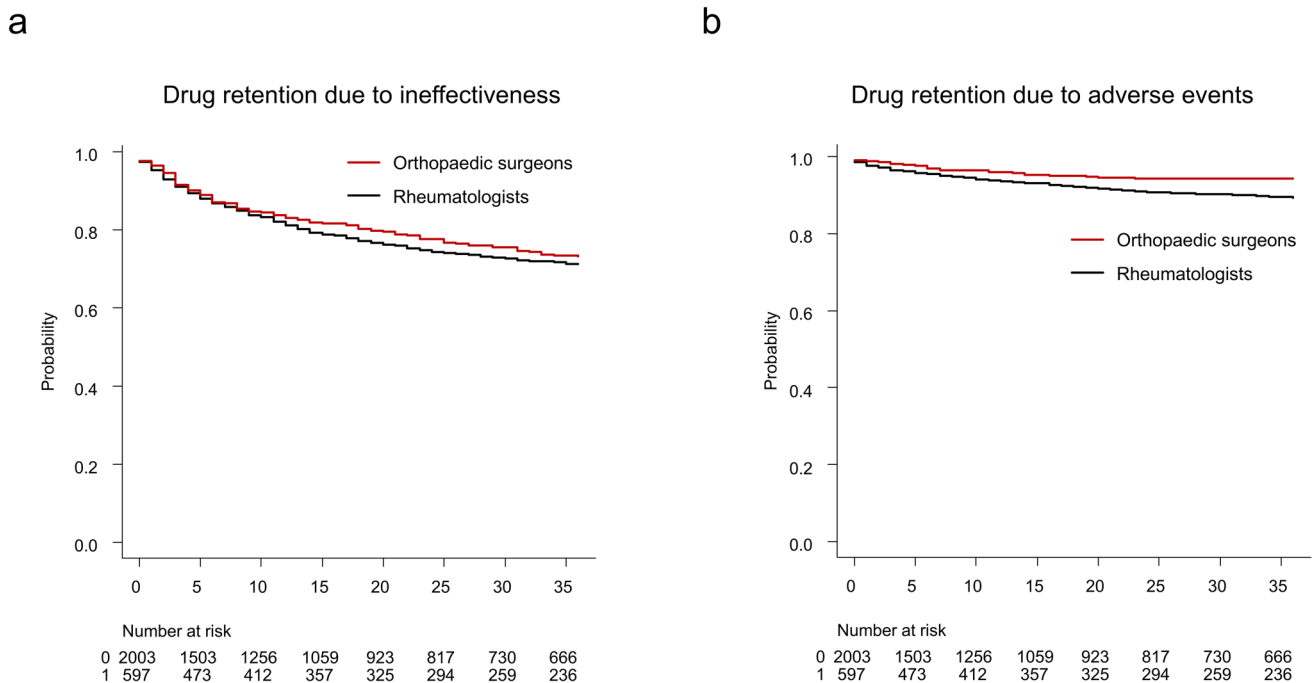
In this multicenter cohort study using the ANSWER registry, we compared patient characteristics, treatment patterns, treatment retention, and disease activity control

**Table 2** Comparison of treatment strategies between groups

Variable	Rheumatologists (n=5436)	Orthopaedic surgeons (n=1832)	P value
Initiated bDMARDs or JAKi			
TNFi (%)	46.9	53.1	<0.001
aIL-6Ra (%)	23.3	20.6	0.015
CTLA4-Ig (%)	17.5	10.2	<0.001
JAKi (%)	12.3	16.2	<0.001
Concomitant treatment			
MTX usage (%)	41.4	46.0	<0.001
MTX dose (mg/week)	9.9±4.8	8.7±3.6	<0.001
GCs usage (%)	33.1	27.0	<0.001
GCs dose (PSL equivalent, mg/day)	5.4±4.4	4.2±2.6	<0.001
Other csDMARDs usage (%)	50.4	38.7	<0.001
Sulfasalazine usage (%)	19.9	16.2	<0.001
Iguratimod usage (%)	13.0	10.8	0.014
Tacrolimus usage (%)	8.6	6.0	<0.001
Bucillamine usage (%)	8.2	3.7	<0.001
Intra-articular GCs injection during follow-up (%)	4.7	14.6	<0.001

Values are presented as mean±standard deviation or percentage. Differences between groups were assessed using the Mann–Whitney *U* test for continuous variables and the chi-square test for categorical variables

*Abbreviations:* aIL-6Ra anti-interleukin-6 receptor antibody, bDMARDs biologic disease-modifying antirheumatic drugs, csDMARDs conventional synthetic disease-modifying antirheumatic drugs, CTLA4-Ig Cytotoxic T-Lymphocyte Antigen 4–Immunoglobulin fusion protein, GCs glucocorticoids, JAKi Janus kinase inhibitor, MTX methotrexate, PSL prednisolone, TNFi tumor necrosis factor inhibitor



**Fig. 2** Kaplan–Meier curves for drug retention by treating department. Kaplan–Meier curves for treatment retention are shown for the rheumatologists group and the orthopaedic surgeons group. **a** Retention due to ineffectiveness. **b** Retention due to adverse events

**Table 3** Adjusted hazard ratios for treatment discontinuation according to reason

Reason for discontinuation	Hazard ratio (reference = rheumatologist group)	95% CI	P value
Ineffectiveness	0.98	0.83–1.17	0.854
Adverse events	0.61	0.46–0.82	0.001
Non-adverse events	0.86	0.66–1.15	0.318
Remission	0.53	0.30–0.93	0.026

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. The rheumatologist group was used as the reference. Models were adjusted for age, sex, disease duration, BMI, RF, and ACPA positivity, concomitant MTX use, concomitant GCs use and other csDMARDs use, initiated drug class (TNFi, aIL-6Ra, CTLA4-Ig, or JAKi), bDMARDs or JAKi-naïve status, and Steinbrocker stage and class, comorbid hypertension, dyslipidemia, diabetes mellitus, baseline eGFR and KL-6. Non-adverse events included patient preference, pregnancy planning, and other non-medical reasons

**Abbreviations:** ACPA anti-cyclic citrullinated peptide antibody, *aIL-6Ra* anti-interleukin-6 receptor antibody, *bDMARDs* biologic disease-modifying antirheumatic drugs, *BMI* body mass index, *CTLA4-Ig* Cytotoxic T-Lymphocyte Antigen 4-Immunoglobulin fusion protein, *eGFR* estimated glomerular filtration rate, *GCs* glucocorticoids, *JAKi* Janus kinase inhibitor, *KL-6* Krebs von den Lungen-6, *MTX* methotrexate, *RF* rheumatoid factor, *TNFi* tumor necrosis factor inhibitor

between RA patients treated by rheumatologists and those treated by orthopaedic surgeons. Patients managed by orthopaedic surgeons had longer disease duration, higher seropositivity for RF and ACPA, and more advanced radiographic and functional impairment. Despite these differences in baseline characteristics and treatment strategies, disease activity improvement after treatment initiation and treatment retention due to ineffectiveness were comparable between the two groups after adjustment for potential confounders. In contrast, treatment discontinuation due to adverse events occurred more frequently among patients managed by rheumatologists.

Historically, both orthopaedic surgeons and rheumatologists have been involved in the pharmacological management of RA in Japan, a system that is relatively uncommon worldwide where RA treatment is usually provided primarily by rheumatologists. In Japan, however, access to rheumatology specialists may be limited in some regions, particularly in rural areas with wide medical catchment regions. In this context, orthopaedic surgeons also contribute to RA care. Importantly, orthopaedic surgeons involved in pharmacological management typically complete formal rheumatology training and are board-certified by the Japan College of Rheumatology or the Japan Orthopaedic Association. All orthopaedic surgeons included in this study were such trained specialists. These results may provide useful insights

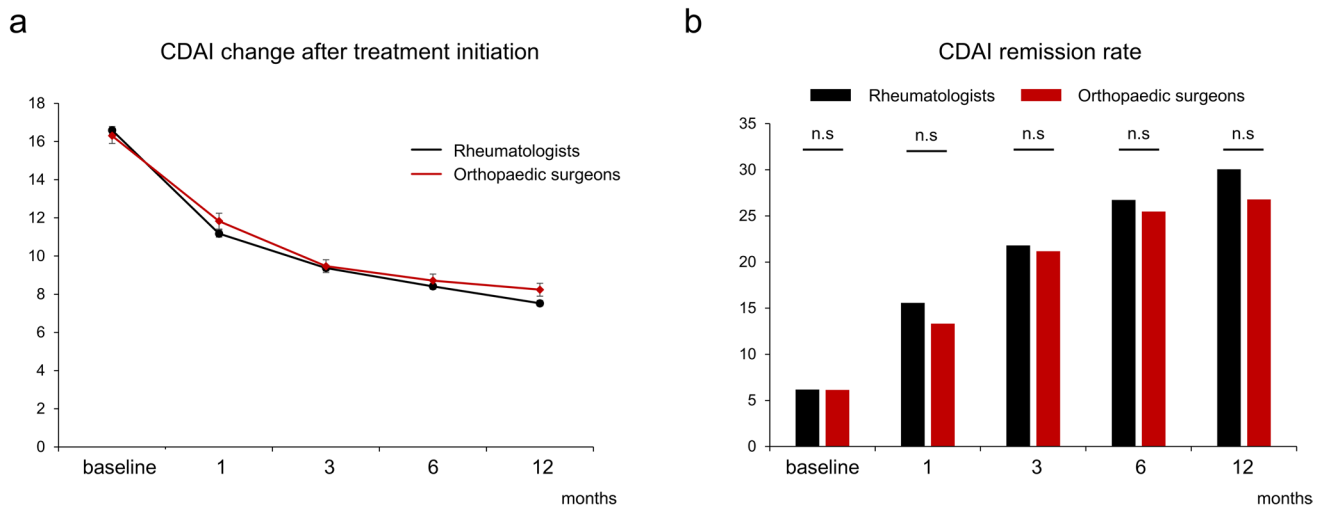
for healthcare systems facing similar challenges in ensuring adequate access to rheumatology care.

Patients treated by orthopaedic surgeons exhibited distinct baseline characteristics compared with those treated by rheumatologists. The orthopaedic surgeon group included a higher proportion of women, a longer disease duration, higher positivity rates for RF and ACPA, and a higher ESR, indicating a predominance of patients with typical seropositive and established RA, consistent with patterns previously reported in the IORRA cohort [5]. This finding may reflect the clinical practice pattern whereby diagnostically challenging cases are referred to rheumatology clinics, whereas patients with more typical rheumatoid arthritis may also be treated in orthopaedic surgery clinics. In addition, some patients may have been referred for surgical evaluation and subsequently continued pharmacological management in orthopaedic surgery clinics, which could partly explain the higher prevalence of advanced radiographic stage and functional impairment in this group.

Regarding treatment strategies, orthopaedic surgeons more frequently prescribed TNFi and JAKi, accompanied by higher rates of MTX use but lower rates of concomitant GCs and other csDMARDs. The higher use of TNFi in the orthopaedic surgery group may be attributable to the higher rate of concomitant MTX use in this group. Although information on comorbidities such as interstitial lung disease was not available, unmeasured patient factors may have influenced treatment selection, including preferential use of CTLA4-Ig in rheumatology clinics.

After adjustment for differences in baseline characteristics and treatment-related factors, treatment retention due to ineffectiveness did not differ significantly between the orthopaedic surgeon group and the rheumatologists group. This finding is noteworthy given that patients in the orthopaedic surgery group had several unfavorable prognostic features, including longer disease duration, lower proportions of bDMARDs or JAKi-naïve patients, and more advanced joint destruction [20, 21]. This result may reflect the widespread implementation of standardized treatment strategies based on current ACR/EULAR and JCR guidelines, which have enabled patients to receive comparable care across different clinical settings. Adherence to these treatment guidelines may therefore play an important role in achieving consistent clinical outcomes regardless of the treating specialty.

In this study, treatment discontinuation due to adverse events was more frequent among patients managed by rheumatologists. Although adjustments were made for comorbid hypertension, dyslipidemia, and diabetes, and baseline KL-6 levels were included as a surrogate for interstitial lung disease, this finding may still reflect



**Fig. 3** Changes in Clinical Disease Activity Index and remission rates after treatment initiation. **a** Mean Clinical Disease Activity Index (CDAI) values from baseline to 12 months after initiation of a biologic disease-modifying antirheumatic drug or Janus kinase inhibitor are shown for the rheumatologists group and the orthopaedic surgeons group. Error bars indicate standard error. **b** CDAI remission rates at each time point from baseline to 12 months after treatment initiation are shown for the rheumatologists group and the orthopaedic surgeons group

residual differences in patient characteristics not fully captured in the registry. Furthermore, the higher burden of comorbidities in the rheumatologist group may have prompted more cautious management, including preventive discontinuation for relatively mild adverse events, thereby lowering the threshold for treatment cessation. Therefore, this observation should be interpreted cautiously and does not necessarily indicate a higher intrinsic safety risk in rheumatology care.

Similarly, treatment discontinuation due to remission was less frequent in the orthopaedic surgeon group. This difference may reflect variations in treatment goals or clinical decision-making between specialties, including differences in the definition of remission, the timing of treatment de-escalation, or physicians' preferences regarding treatment continuation. Therefore, this finding may represent differences in clinical management rather than true differences in treatment effectiveness.

Several limitations of this study should be acknowledged. First, information on important comorbidities, such as interstitial lung disease and other connective tissue diseases, was not available in the registry, which may have influenced both treatment selection and adverse event–related discontinuation. Second, information on surgical procedures performed during follow-up was not available; therefore, the potential impact of surgery on disease activity could not be evaluated. Third, detailed information on adverse events was not available for all treatment courses. Fourth, this study included only patients receiving phase II or phase III therapy with bDMARDs or JAKi; therefore, patients treated with csDMARDs alone were not evaluated, and the findings may not represent all patients managed in orthopaedic surgery or rheumatology clinics.

Fifth, the ANSWER cohort consists of patients treated at large hospitals in the Kansai region of Japan, which may limit the generalizability of the findings to other clinical settings or healthcare systems.

Despite these limitations, this study provides clinically important and novel insights by demonstrating that bDMARDs and JAKi therapy delivered by orthopaedic surgeons is not associated with inferior treatment retention or disease activity control compared with rheumatology clinics in real-world clinical practice.

Conclusions

## Conclusions

In this multicenter cohort study, treatment retention and disease activity control with bDMARDs and JAKi therapy were comparable between patients managed by orthopaedic surgeons and rheumatologists. These findings suggest that, with guideline-based treatment, patients treated by orthopaedic surgeons can achieve clinical outcomes comparable to those in rheumatology clinics.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s10067-026-08061-7>.

**Acknowledgements** We thank all the medical staff at all the institutions who participated in the ANSWER cohort for providing the data.

**Author contribution** Y.E.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, visualization, and writing—original draft. Y.O., K.T., T.N., K.M., T.F., I.S., M.Y., K. Nagai., A.Y., M.H., T.O., Y.N., T.I., Y.S.,

and H.M.: resources. W.Y.: data curation. T.N., A.K., S.O., and K. Nakata.: supervision. K.E.: conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation, and writing—review and editing.

**Funding** Open Access funding provided by The University of Osaka. The study reported in this publication uses the ANSWER Cohort, was supported by grants from 12 pharmaceutical companies (AbbVie GK, Asahi-Kasei, Ayumi, Chugai, Eisai, Eli Lilly, Janssen K.K., Ono, Sanofi K.K., Taisho, Teijin Healthcare, and UCB Japan) and an information technology service company (CAC). This study was conducted as an investigator-initiated study. These companies had no roles in the study design, data collection, data analysis, data interpretation, or writing of the report.

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

## Declarations

**Ethics approval and consent to participate** The representative facility for this registry was Kyoto University. This observational study was conducted following the Declaration of Helsinki and approved by the ethics committees of the following seven institutes: Kyoto University (granted on 2016-03-24/approval No. R053), Osaka University (granted on 2015-11-04/approval No. 15300), Osaka Metropolitan University (granted on 2021-6-09/approval No. 2021-074), Osaka Medical and Pharmaceutical University (granted on 2014-07-14/approval No. 1529), Kansai Medical University (granted on 2017-11-21/approval No. 2014625), Kobe University (granted on 2015-03-20/approval No. 1738), Nara Medical University (granted on 2018-01-23/approval No. 1692), and Osaka Red Cross Hospital (granted on 2015-09-01/approval No. 644). Written informed consent was obtained from the participants. The ethics committee at Osaka University Hospital waived the requirement for patient informed consent by posting the opt-out information on the hospital's homepage.

**Consent for publication** Written informed consent to publish the study results was obtained from all patients.

**Competing interests** Y.E. and K.E. are affiliated with the Department of Sports Medical Biomechanics, The University of Osaka Graduate School of Medicine Faculty of Medicine, which is supported by Asahi-Kasei.

Y.E. has received a speaker fee from Amgen, Asahi-Kasei, Ayumi, Daiichi-Sankyo, Eisai, Taisho, and UCB Japan. Y.O. has received speaker fees from Eli Lilly, Nippon Boehringer Ingelheim, Pfizer, Asahi-Kasei, Ono Pharmaceutical, Mitsubishi-Tanabe, Taisho, and Novartis Pharma. K.M. is affiliated with a department that is financially supported by two pharmaceutical companies (Asahi-Kasei and Ayumi) and the city government (Nagahama City) and received a research grant from Daiichi-Sankyo and a speaker fee from AbbVie, Asahi-Kasei, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Bristol-Myers Squibb, and Pfizer. T.F. is affiliated with a department that is financially supported by two pharmaceutical companies (Asahi-Kasei and Ayumi) and the city government (Nagahama City) and has received a speaker fee from Asahi-Kasei, AbbVie, Janssen, Mitsubishi-Tanabe, and Eisai. M.H. has received research grants and/or a speaker fee from Asahi Kasei, Astellas, AstraZeneca, Ayumi Pharma, Bristol Meyers, Chugai, Eisai, Eli Lilly, Gilead Sciences Japan, Janssen pharma, Ono Pharma, Ohtsuka Pharma, Taisho Pharma, Tanabe Mitsubishi, UCB Japan. T.O. received a research grant from AbbVie, Asahi-Kasei, Chugai, Eisai, Eli Lilly and Mitsubishi-Tanabe and a speaker fee from AbbVie, Chugai, Eli Lilly, Janssen, and Novartis Pharma. T.K. is affiliated with a department that is financially supported by six pharmaceutical companies (Mitsubishi-Tanabe, Asahi-

Kasei, AbbVie, Chugai, Eisai, and Takeda) and has received payments for lectures from AbbVie, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, Pfizer, and Boehringer Ingelheim. Y.N. has received speaker fees from Astellas Pharma, Asahi Kasei Pharma, Eisai, Eli Lilly, AstraZeneca, and Tanabe Pharma. Y.S. has received speaking fees from Pfizer, Chugai., Janssen Pharmaceutical K.K., Eisai, and AbbVie. A.K. has received a research grant from Chugai and a speaker fee from Chugai, Eisai, Mitsubishi-Tanabe, AbbVie, and Ono Pharmaceutical.

K. Nakata. has received a research grant from Astellas and supervises the Department of Sports Medical Biomechanics, The University of Osaka Graduate School of Medicine Faculty of Medicine, which is supported by Asahi-Kasei. K.E. has received research grants from Asahi-Kasei and Teijin Pharma. K.E. has received a speaker fee from AbbVie, Amgen, Argenx, Asahi-Kasei, Astellas, Ayumi, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Janssen, Mitsubishi-Tanabe, Ono Pharmaceutical, Pfizer, Sanofi, Taisho, Teijin Pharma, and UCB Japan. The remaining authors have declared no conflicts of interest.

**Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

- Harrington R, Al Nokhatha SA, Conway R (2020) Jak inhibitors in rheumatoid arthritis: an evidence-based review on the emerging clinical data. *J Inflamm Res* 13:519–531
- Favalli EG, Maioli G, Caporali R (2024) Biologics or janus kinase inhibitors in rheumatoid arthritis patients who are insufficient responders to conventional anti-rheumatic drugs. *Drugs* 84(8):877–894
- Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D et al (2023) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 82(1):3–18
- Harigai M, Kaneko Y, Tanaka E, Hirata S, Kameda H, Kaneko K et al (2025) 2024 update of the Japan college of rheumatology clinical practice guidelines for the management of rheumatoid arthritis: secondary publication. *Mod Rheumatol* 35(3):387–401
- Momohara S, Inoue E, Ikari K, Yano K, Tokita A, Honjo Y et al (2012) Comparison of characteristics and therapeutic efficacy in rheumatoid arthritis patients treated by rheumatologists and those treated by orthopedic surgeons under a team medicine approach at the same institute. *Mod Rheumatol* 22(2):209–15
- Yamanaka H, Tanaka E, Nakajima A, Furuya T, Ikari K, Taniguchi A et al (2020) A large observational cohort study of rheumatoid arthritis, IORRA: providing context for today's treatment options. *Mod Rheumatol* 30(1):1–6
- Hyrich KL, Watson KD, Lunt M, Symmons DP (2011) Changes in disease characteristics Hyrich KL, Watson KD, Lunt M, Symmons DP. Changes in disease characteristics Hyrich KL, Watson KD, Lunt M, Symmons DP. Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis

- factor therapy for rheumatoid arthritis between 2001 and 2008. *Rheumatology (Oxford)* 50(1):117–23
8. Murata K, Uozumi R, Hashimoto M, Ebina K, Akashi K, Onishi A et al (2022) The real-world effectiveness of anti-RANKL antibody denosumab on the clinical fracture prevention in patients with rheumatoid arthritis: the ANSWER cohort study. *Mod Rheumatol* 32(4):834–838
  9. Ebina K, Hirano T, Maeda Y, Okita Y, Etani Y, Hirao M et al (2023) Add-on effectiveness of methotrexate or iguratimod in patients with rheumatoid arthritis exhibiting an inadequate response to Janus kinase inhibitors: the ANSWER cohort study. *Mod Rheumatol* 33(4):690–699
  10. Makino H, Kotani T, Hata K, Nishioka D, Yamamoto W, Yoshikawa A et al (2023) Prognostic factors affecting respiratory-related death in patients with rheumatoid arthritis complicated by interstitial lung disease: an ANSWER cohort study. *Mod Rheumatol* 33(5):928–35
  11. Etani Y, Okita Y, Maeda Y, Tsujimoto K, Hirao M, Onishi A et al (2025) Distinct impact of RF and ACPA titre on the effectiveness and persistency of biologics and JAK inhibitors: the ANSWER cohort study. *Mod Rheumatol* 35(5):820–9
  12. Arnett FC, Edworthy SM, Bloch DA, Mcshane DJ, Fries JF, Cooper NS et al (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 31(3):315–24
  13. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al (2010) Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Annals of the Rheumatic Diseases*. 69(9):1580–8
  14. Ebina K, Etani Y, Maeda Y, Okita Y, Hirao M, Yamamoto W et al (2023) Drug retention of biologics and Janus kinase inhibitors in patients with rheumatoid arthritis: the ANSWER cohort study. *RMD Open*. <https://doi.org/10.1136/rmdopen-2023-003160>
  15. Favalli EG, Biggioggero M, Marchesoni A, Meroni PL (2014) Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies. *Rheumatology* 53(9):1664–1668
  16. Gabay C, Riek M, Scherer A, Finckh A, physicians obotSc (2015) Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry. *Rheumatology*. 54(9):1664–72
  17. Jørgensen TS, Kristensen LE, Christensen R, Bliddal H, Lorenzen T, Hansen MS et al (2015) Effectiveness and drug adherence of biologic monotherapy in routine care of patients with rheumatoid arthritis: a cohort study of patients registered in the Danish biologics registry. *Rheumatology* 54(12):2156–65
  18. Ebina K, Hirano T, Maeda Y, Yamamoto W, Hashimoto M, Murata K et al (2020) Drug retention of 7 biologics and tofacitinib in biologics-naïve and biologics-switched patients with rheumatoid arthritis: the ANSWER cohort study. *Arthritis Res Ther* 22(1):142
  19. Kanda Y (2013) Investigation of the freely available easy-to-use software ‘EZ’ for medical statistics. *Bone Marrow Transplant* 48(3):452–458
  20. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M et al (2014) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 73(3):492–509
  21. Nagy G, Roodenrijs NMT, Welsing PM, Kedves M, Hamar A, van der Goes MC et al (2021) EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 80(1):31–5

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## Authors and Affiliations

Yuki Etani<sup>1</sup> · Yasutaka Okita<sup>2</sup> · Kohei Tsujimoto<sup>2</sup> · Takaaki Noguchi<sup>3</sup> · Koichi Murata<sup>4,5</sup> · Takayuki Fujii<sup>4,5</sup> · Iku Shirasugi<sup>6</sup> · Mai Yamashita<sup>6</sup> · Koji Nagai<sup>7</sup> · Ayaka Yoshikawa<sup>7</sup> · Motomu Hashimoto<sup>8</sup> · Tadashi Okano<sup>9</sup> · Yuji Nozaki<sup>10</sup> · Tetsu Itami<sup>10</sup> · Yonsu Son<sup>11</sup> · Hidehiko Makino<sup>11</sup> · Wataru Yamamoto<sup>12</sup> · Atsushi Kumanogoh<sup>2</sup> · Seiji Okada<sup>3</sup> · Ken Nakata<sup>13</sup> · Kosuke Ebina<sup>1,3</sup>

✉ Kosuke Ebina  
k-ebina@ort.med.osaka-u.ac.jp

<sup>1</sup> Department of Sports Medical Biomechanics, The University of Osaka Graduate School of Medicine Faculty of Medicine, Suita, Japan

<sup>2</sup> Department of Respiratory Medicine and Clinical Immunology, The University of Osaka Graduate School of Medicine Faculty of Medicine, Suita, Japan

<sup>3</sup> Department of Orthopaedic Surgery, The University of Osaka Graduate School of Medicine Faculty of Medicine, Suita, Japan

<sup>4</sup> Department of Advanced Medicine for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan

<sup>5</sup> Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

<sup>6</sup> Department of Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Kobe, Japan

<sup>7</sup> Department of Internal Medicine (IV), Osaka Medical and Pharmaceutical University, Takatsuki, Japan

<sup>8</sup> Department of Clinical Immunology, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan

<sup>9</sup> Center for Senile Degenerative Disorders (CSDD), Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

<sup>10</sup> Department of Hematology and Rheumatology, Kindai University School of Medicine, Sakai, Japan

<sup>11</sup> First Department of Internal Medicine, Kansai Medical University, Osaka, Hirakata, Japan

<sup>12</sup> Department of Health Information Management, Kurashiki Sweet Hospital, Kurashiki, Japan

<sup>13</sup> Department of Health and Sport Sciences, The University of Osaka Graduate School of Medicine Faculty of Medicine, Suita, Japan