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ORIGINAL RESEARCH

Real-World Safety and Efficacy of Targeted Therapies in Rheumatoid Arthritis: A 5-Year, 5130-Case Follow-Up from FIRST Registry

Koshiro Sonomoto · Shingo Nakayamada · Hiroaki Tanaka · Atsushi Nagayasu · Yoshiya Tanaka

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ABSTRACT

Introduction: This work aims to illustrate the evolution and ongoing challenges of rheumatoid arthritis (RA) management with targeted therapy over 20 years, using a cohort study from the world's oldest society.

Methods: Data were obtained from FIRST registry, a multicenter cohort of patients with RA treated with biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs). Patients were followed for 60 months and assessed for drug efficacy, retention, and reasons for discontinuation.

Results: Analysis of 5130 treatments over 16,616 person-years revealed shifts in strategies and demographics. Despite an aging population (51.9–64.3 years) with increasing comorbidities (lung disease: 11.1–36.2%, malignancy: 2.2–13.1%), b/tsDMARD use expanded to include patients with lower disease activity. With better disease control, discontinuations due to adverse events decreased, and particularly infections fell from 2.1 to 0.7 per 100 person-years. Remission rates improved over time in the naïve group but remained largely unchanged in the prior b/tsDMARDs group. Retention rates varied by bDMARD class, with TNF inhibitors (TNFi) showing a decrease over time and IL-6 receptor inhibitors (IL-6Ri) and CTLA4-Ig showing an increase in retention. TNFi had high remission rates but low retention, whereas CTLA4-Ig and IL-6Ri had lower remission rates and higher retention. Changes in functional improvement were modest overall, and in patients aged 75 years and older, functional gains remained limited.

Conclusions: The study highlights the evolving landscape of RA management in an aging society, noting gains in efficacy and safety. However, unmet needs persist, particularly for patients not fully achieving treat-to-target goals and those with limited functional improvement.

Keywords: Rheumatoid arthritis; Biologic/targeted synthetic disease-modifying antirheumatic drugs; Cohort study

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K. Sonomoto
Department of Clinical Nursing, School of Health Sciences, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

K. Sonomoto · S. Nakayamada · H. Tanaka · A. Nagayasu · Y. Tanaka (✉)
The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
e-mail: tanaka@med.uoeh-u.ac.jp

Key Summary Points

Why carry out this study?

Advances in rheumatoid arthritis (RA) treatment have improved disease activity control; however, functional improvement remains limited: this study aimed to confirm these findings in a cohort from the world's oldest society.

What was learned from the study?

FIRST registry demonstrated improved disease control with fewer adverse events in a super-aged population with increased comorbidities.

Despite these benefits, it confirmed inadequate improvement in physical function, particularly in patients aged 75 years and older.

TNF inhibitors showed higher remission rates but lower retention rates compared to IL-6 receptor inhibitors and CTLA4-Ig, suggesting that the latter may include difficult-to-treat patients.

The study reaffirms the need for new drug development and highlights the importance of a comprehensive approach, including non-drug interventions.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by synovitis, which leads to joint destruction, physical disability, and excess mortality [1]. To prevent these consequences, therapeutic approaches have continuously evolved, with guidelines being frequently updated worldwide [2–4]. In Japan, the era of targeted molecular therapy began with infliximab in 2003. By the end of 2023, 14 originator biologics (infliximab, etanercept, tocilizumab, adalimumab, abatacept, golimumab, certolizumab pegol, tofacitinib, baricitinib, sarilumab, peficitinib, upadacitinib, filgotinib, and ozoralizumab, listed in order of approval) and several biosimilars became available. With the implementation of a treat-to-target (T2T) strategy and diverse treatment options, approximately half of patients with RA can now achieve remission [5].

With the rapid global aging process, Japan has become one of the fastest-aging countries, reaching a super-aged society with over 21% of the population aged 65 years or older in 2007 [6], and this trend is expected to continue. As society has aged, the demographics of patients with RA have shifted. RA has traditionally been more common in women aged 30s–50s. However, societal aging, decreased mortality [7, 8], and the rising age of RA onset [8, 9] have led to the elderly now constituting the majority of patients with RA [10], presenting new challenges in management. Many of these patients have a greater risk of comorbidities such as malignancy, infection, osteoporosis, chronic kidney disease, and lung disease [11], which complicates RA management.

Japan has continuously searched for the optimal RA management in this unprecedented aging society. While management has evolved through trial-and-error with the development of drugs, the experiences of the super-aged society certainly provide valuable insights for other countries facing aging populations. The purpose of this study was to explore the advances and challenges in RA management in an aging population. Using descriptive analysis, we outlined changes in patient demographics and treatment retention rates since the introduction of biologics, ultimately aiming to identify areas for further improvement.

METHODS

Data Source

Participants in this study were recruited from FIRST registry, which includes patients with RA treated with biologic/targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) at University Hospital of the University of Occupational and Environmental Health, Japan (UOEH) and 28 other institutions in nine municipalities. The study analyzed data from

August 2003 through December 2023. Patients who met American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) 2010 RA classification criteria and did not respond to phase I therapy were referred to UOEH for further evaluation to determine their eligibility for b/tsDMARDs. This evaluation included the assessment of contraindications and comorbidities, including screening for comorbidities, such as infections and malignancies [12]. Eligibility was carefully assessed, including assessment of indications, contraindications, and patient willingness, in accordance with regulations, package inserts, and relevant guidelines [2–4]. FIRST registry has no exclusion criteria to better reflect real-world practice; therefore, all patients starting b/tsDMARDs were invited to participate and those who agreed were enrolled after providing informed consent. FIRST registry is treatment-based rather than case-based, with each switch to a different b/tsDMARD recorded as a new entry, but each product is counted only once per patient. As part of FIRST registry, patients starting b/tsDMARD treatment will typically continue to be treated locally and will return to UOEH for assessments at 6 months, 1 year and annually thereafter. During these visits, clinical information is collected, including RA disease activity, comorbidities, and treatment status. Patients who do not wish to visit UOEH can have these assessments carried out by local specialists who can provide the information to UOEH. Therefore, this registry operates as a multicenter system. The term b/tsDMARDs includes tumor necrosis factor inhibitors (TNFi: infliximab and its biosimilar, etanercept and its biosimilar, adalimumab and its biosimilar, golimumab, certolizumab pegol, and ozoralizumab), interleukin-6 receptor inhibitors (IL-6Ri: tocilizumab and sarilumab), cytotoxic T-lymphocyte-associated protein 4 immunoglobulin (CTLA4-Ig: abatacept), and Janus kinase inhibitors (JAKi: tofacitinib, baricitinib, peficitinib, upadacitinib, and filgotinib). Notably, rituximab and anakinra are not approved for the treatment of RA in Japan and are therefore not included in FIRST registry.

Study Design and Definition of b/tsDMARD Eras

To assess the evolution of RA management, we divided the study period into four eras based on the introduction of key b/tsDMARDs. These eras are defined as Era 1 (TNF era: from the introduction of infliximab in 2003, including infliximab and etanercept), Era 2 (IL-6 era: beginning with tocilizumab in 2008, including tocilizumab, adalimumab, and agents introduced in Era 1), Era 3 (CTLA4 era: marked by the approval of abatacept in 2010, including abatacept, golimumab, certolizumab pegol, and agents from Eras 1 and 2), and Era 4 (JAK era: beginning with tofacitinib in 2013, including tofacitinib, baricitinib, sarilumab, peficitinib, upadacitinib, filgotinib, ozoralizumab and all agents from Eras 1–3). This categorization allowed us to examine the impact of these advances on RA treatment and patient outcomes over different time periods. It is also important to note the approved increase in methotrexate dose from 8 to 16 mg/week in February 2011. When discussing the age group, we stratified the population to Adult (– 64 years), Young-old (65–74 years), and Senior (75 + years) according to the Japanese law "Act on Assurance of Medical Care for Elderly People" and our previous report [13].

Selection of b/tsDMARDs for Patients in FIRST Registry

The management strategy in FIRST registry has changed over time. The current strategy is described elsewhere [14]. Briefly, the first step in b/tsDMARD treatment is comprehensive risk management [12]. The physician recommends appropriate prophylaxis and select b/tsDMARDs based on patient risk factors. The physician will recommend vaccinations for pneumococcus, influenza, herpes zoster, and considers anti-*Pneumocystis* pneumonia (PCP) agents such as trimethoprim-sulfamethoxazole, pentamidine, or atovaquone for all patients. Infection risk is a primary consideration in agent selection, with abatacept typically recommended for patients at high risk of infection. Next, patients with

a history of malignancy are considered for IL-6Ri [15]. The concomitant use of methotrexate (MTX) is then evaluated. Patients and their prescribing physicians decided whether to choose treatment with all b/tsDMARDs or b/tsDMARDs without TNFi, taking into account MTX use and dose. Currently, JAKis are less commonly used as first-line b/tsDMARDs. Before the ORAL Surveillance trial [16], however, they were often considered first-line, especially for patients with highly active disease. This stepwise approach aims to tailor treatment decisions to each patient's risk factors, balancing safety and efficacy.

As-Enrolled Analysis and Per-protocol Analysis in this Study

FIRST registry is a treatment-based registry, where treatment-switching treatments is considered a censoring event. In this study, the *"as-enrolled analysis"* stratifies patients based on the treatment regimen they received at enrollment and evaluates outcomes for all patients who started treatment. The *"per-protocol analysis"* also stratifies patients based on their initial treatment regimen but evaluates outcomes only for those who remain on the same treatment at each time point. Missing data were not imputed; however, patients with missing clinical disease activity index (CDAI) data were treated as non-responders in the as-enrolled analysis. The missing table is provided as Table S1 (Era 4 includes a subset of patients who were enrolled within recent years and therefore have not yet reached the 6-month, 1-year, 2-year, 3-year, or 5-year follow-up, resulting in a decreasing population size over longer time periods).

Tools Used in the Analysis

Graphs were generated using Python (with NumPy, Pandas, Matplotlib, Seaborn, Cartopy, Lifelines packages and with the Datetime module) in Google Colaboratory and Prism 9 software.

Ethical Approval

This study followed the Declaration of Helsinki and was approved by the Ethics Committee of the University of Occupational and Environmental Health School of Medicine (#UOEHCRB21-068). Informed consent was obtained from all participants based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese Ministry of Health, Labor and Welfare. Written informed consent was obtained from participants enrolled after April 2015, and written or verbal consent was obtained from others.

RESULTS

Changing RA Treatment Patterns and Patient Profiles

A total of 5130 treatments involving 3494 patients (16,616 person-years) were evaluated. Supplementary Material Fig. S1 shows the geographic distribution of patients enrolled in FIRST registry, which includes six prefectures within a 150-km radius of UOEH. Overall, the trends in RA treatment changed markedly over time (Supplementary Material Figure S2). Until around 2018, TNFi was predominantly used as the first-line b/tsDMARD, while IL-6Ri became more common in recent years (Supplementary Material Figure S2B, left). This shift was also seen in patients with prior b/tsDMARDs, where JAKi and IL-6Ri became the preferred options. Although JAKi was used as a first-line treatment until 2019, its use shifted primarily to switching therapies (Supplementary Material Figure S2B, left and right).

Concurrently, drastic changes were observed in patient demographics (Fig. 1 and Table 1). As the years progressed, the age at initiation or switching of b/tsDMARDs increased from 51.9 years in 2003 to 64.3 years in 2023, while eGFR decreased from 98.3 to 73.7 ml/min. The prevalence of comorbidities such as lung disease (11.1–36.2%), fragility fractures (4.4–20.8%), history of pneumonia (2.2–11.1%), history of

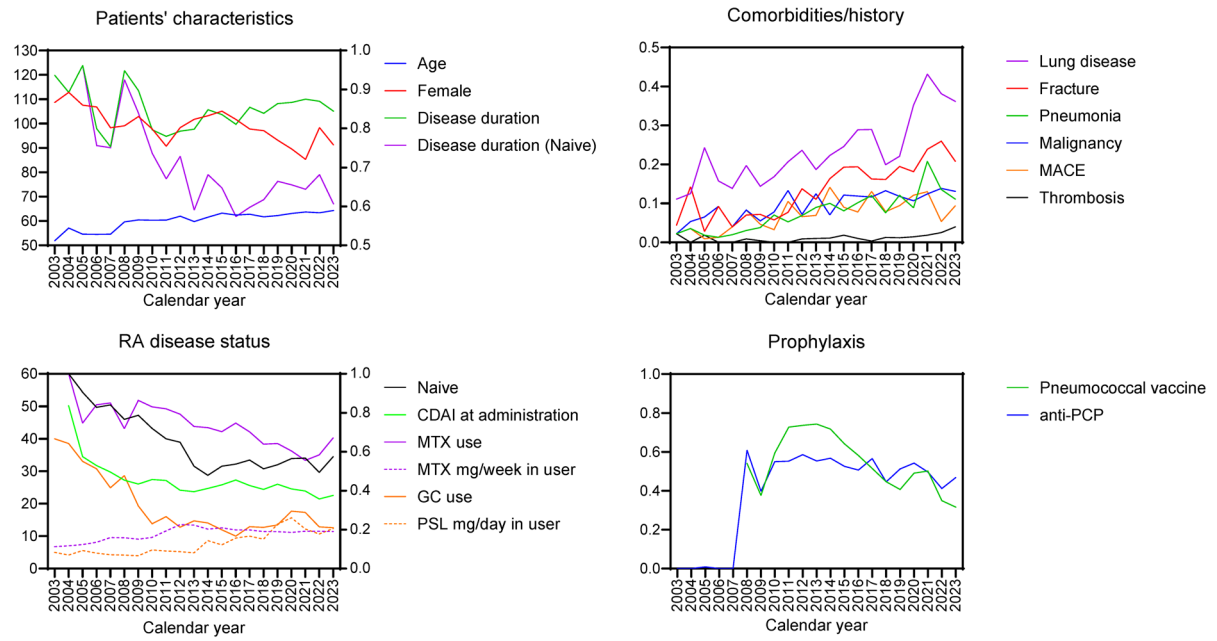


Fig. 1 Twenty-year trends in various aspects of patient characteristics: patient characteristics, comorbidities, rheumatoid arthritis (RA) disease status, and prophylaxis. *MACE* major adverse cardiovascular events, *CDAI* clinical disease activity index, *MTX* methotrexate, *GC* glucocorticoid, *PSL* GC dose in prednisolone equivalent, *PCP* pneumocystis pneumonia

malignancy (2.2–13.1%), major adverse cardiovascular events (MACE: 2.2–9.4%), and thrombosis (2.2–4.0%) also increased, highlighting the increasing complexity of patient profiles with RA. During the infliximab era (2003–2004, before etanercept was approved in 2005), concomitant MTX use was 100%. However, this rate gradually decreased to 67.2% by 2023, even as the average dose increased from 6.8 to 11.4 mg/week (the approved dose of MTX in Japan was raised from 8 to 16 mg/week in 2011). Concomitant glucocorticoid (GC) use decreased markedly from 66.7 to 21.1%. Prophylactic use against pneumococcus and pneumocystis increased sharply from 2008 and has since stabilized at around 40–50%. The time from RA onset to initiation of the first b/tsDMARDs has gradually shortened, with the average duration decreasing from 119.8 to 67.6 months and the mean CDAI at initiation decreasing from 31.9 to 24.6 (Fig. 1, Table 1). This reduction in the time to first b/tsDMARD initiation occurred across all age groups (Supplementary Material Figure S3). However, older patients still experienced longer delays, with a gap of approximately 3 years between the Adult and Senior groups. The background characteristics of b/tsDMARD-naïve patients and those with prior b/tsDMARD exposure were quite similar, with the exception of disease duration and history of fractures and pneumonia (Supplementary Material Figures S4 and 5). Over time, IL-6Ri and CTLA4-Ig were used more frequently in older patients, while TNFi were more commonly used in younger patients (Supplementary Material Table S2). The TNFi group has higher eGFR and higher MTX use, while the IL-6Ri and CTLA4-Ig groups have lower eGFR and lower MTX use. This probably reflects the efficacy of IL-6Ri and CTLA4-Ig as monotherapy, making them suitable for patients with reduced renal function and/or those intolerant to MTX (Supplementary Material Table S2). In summary, despite an aging patient population and increasing comorbidities, b/tsDMARDs were administrated earlier and at lower disease activity, reflecting the broader adoption of these therapies over time.

Table 1 Patients' characteristics across four eras

	Era 1 (TNF) (*N* = 432)	Era 2 (IL-6) (*N* = 611)	Era 4 (CTLA4) (*N* = 858)	Era 4 (JAK) (*N* = 3229)
Age	55.7 ± 13.8	59.7 ± 14.5	61.2 ± 14.1	62.7 ± 14.1
Female (%)	83.1	81.7	79.3	79.0
BMI	21.4 ± 3.3	21.7 ± 3.7	22.2 ± 3.8	22.6 ± 4.1
eGFR (ml/min)	91.2 ± 27.0	89.3 ± 31.5	85.2 ± 29.7	76.7 ± 25.8
Smoking (Never/Current/Past, %)	79/13/8	77/12/11	74/12/14	62/14/24
RA duration (months)	108.3 ± 113.8	109.3 ± 127.6	97.9 ± 112.0	106.1 ± 120.0
RA stage (I/II/III/IV, %)	12/42/21/25	19/43/19/19	21/43/20/16	27/42/17/14
b/tsDMARDs naïve (%)	89.6	76.1	62.9	53.6
RF positive (%)	86.3	81.5	78.0	76.9
ACPA positive (%)	74.4	80.5	75.9	72.4
CDAI	31.9 ± 13.9	26.7 ± 13.9	25.2 ± 13.1	24.6 ± 12.8
MTX use (%)	85.2	81.5	78.9	65.7
GC use (%)	53.2	32.9	23.7	22.8
MTX (mg/week)	8.0 ± 2.1	9.5 ± 2.6	12.6 ± 3.5	11.8 ± 3.8
GC (mg/day)	4.8 ± 2.7	4.6 ± 6.6	4.9 ± 5.4	11.0 ± 13.7
Past pneumonia (%)	17.6	15.9	21.4	29.8
Lung disease (%)	2.3	4.4	7.2	11.4
Malignancy (%)	5.3	7.4	10.5	12.0

TNF tumor necrosis factor, *IL-6* interleukin-6, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *JAK* Janus kinase, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein/peptide antibody, *CDAI* clinical disease activity index, *MTX* methotrexate, *GC* glucocorticoid

Retention Trends and Discontinuation Reasons

To further understand the evolution of management, we next evaluated the 60-month drug retention rates with different reasons for discontinuation (Fig. 2). Data included all-cause discontinuation, discontinuation excluding remission, discontinuation excluding both remission and other reasons, discontinuation due to infection, non-infectious adverse events (AEs), inefficacy, remission, and other reasons. Because discontinuation due to remission or other reasons (e.g., stopping b/tsDMARDs for conception) biases the retention rate downward, this study employed retention rates that exclude discontinuation due to remission and other reasons for evaluation. Retention rates, excluding discontinuations due to remission and other reasons, gradually decreased from Era 1 to Era 3 and recovered in Era 4 (Fig. 2). Inefficacy was the most common reason for discontinuation, increasing over time but improving in Era 4. In contrast, discontinuations due to infection were higher in Era 1 and decreased in

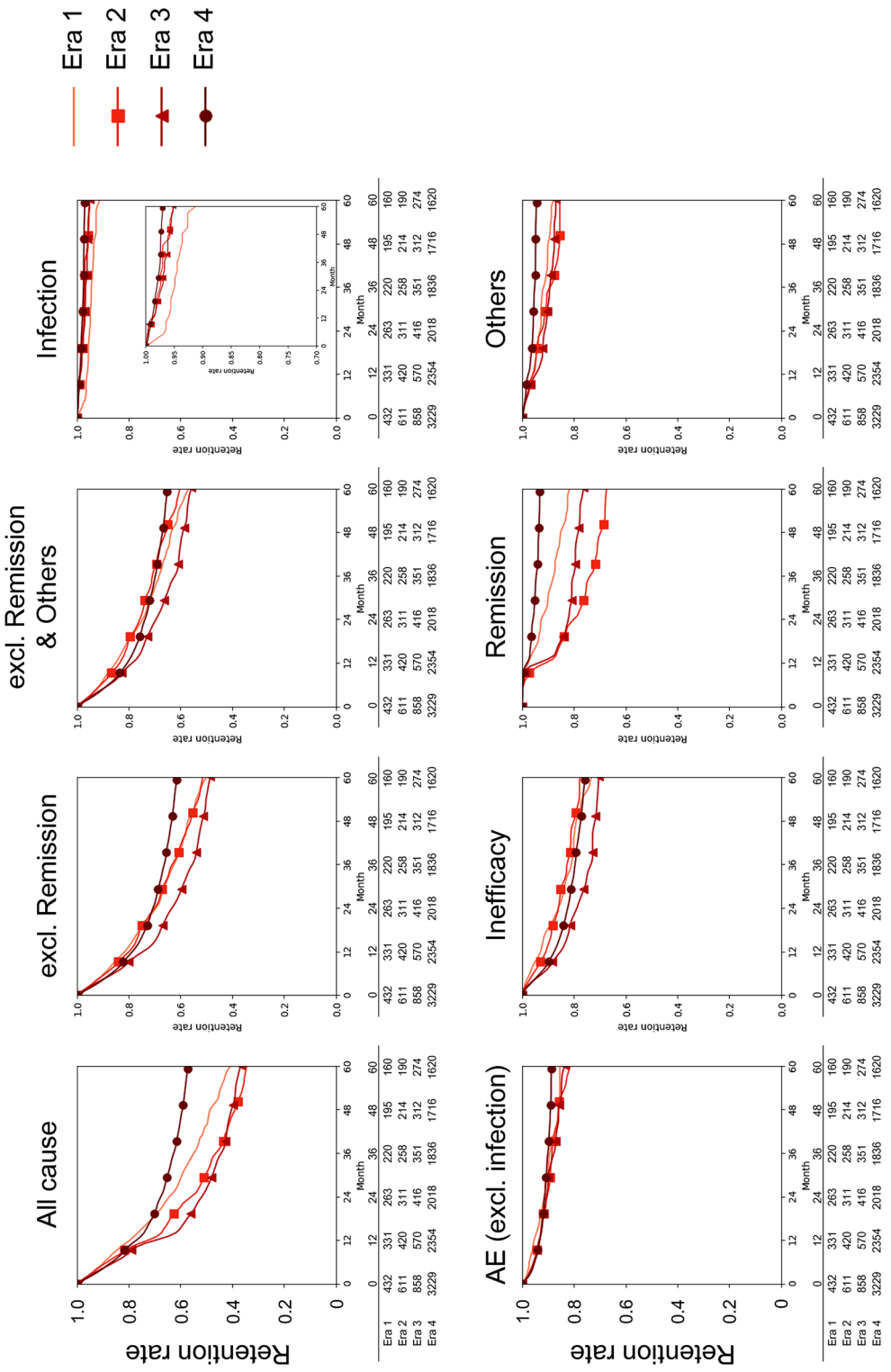


Fig. 2 Five-year drug retention and reasons for discontinuation of b/tsDMARDs across four eras. The Kaplan–Meier plots represent specific discontinuation reasons. The graphs compare changes in 5-year drug retention over four different time periods. *Infection* includes a nested version with the *y*-axis adjusted to [0.7–1.0] for better visualization. *Others* includes discontinuation due to socioeconomic factors, trying to conceive, self-discontinuation, patient request, comorbidities unrelated to rheumatoid arthritis (RA), and death unrelated to RA. *b/tsDMARDs* biologic/targeted synthetic disease-modifying antirheumatic drugs, *AE* adverse event. *Era 1* tumor necrosis factor (TNF) era, *Era 2* interleukin-6 (IL-6) era, *Era 3* cytotoxic T-lymphocyte-associated protein 4 (CTLA4) era, *Era 4* Janus kinase (JAK) era

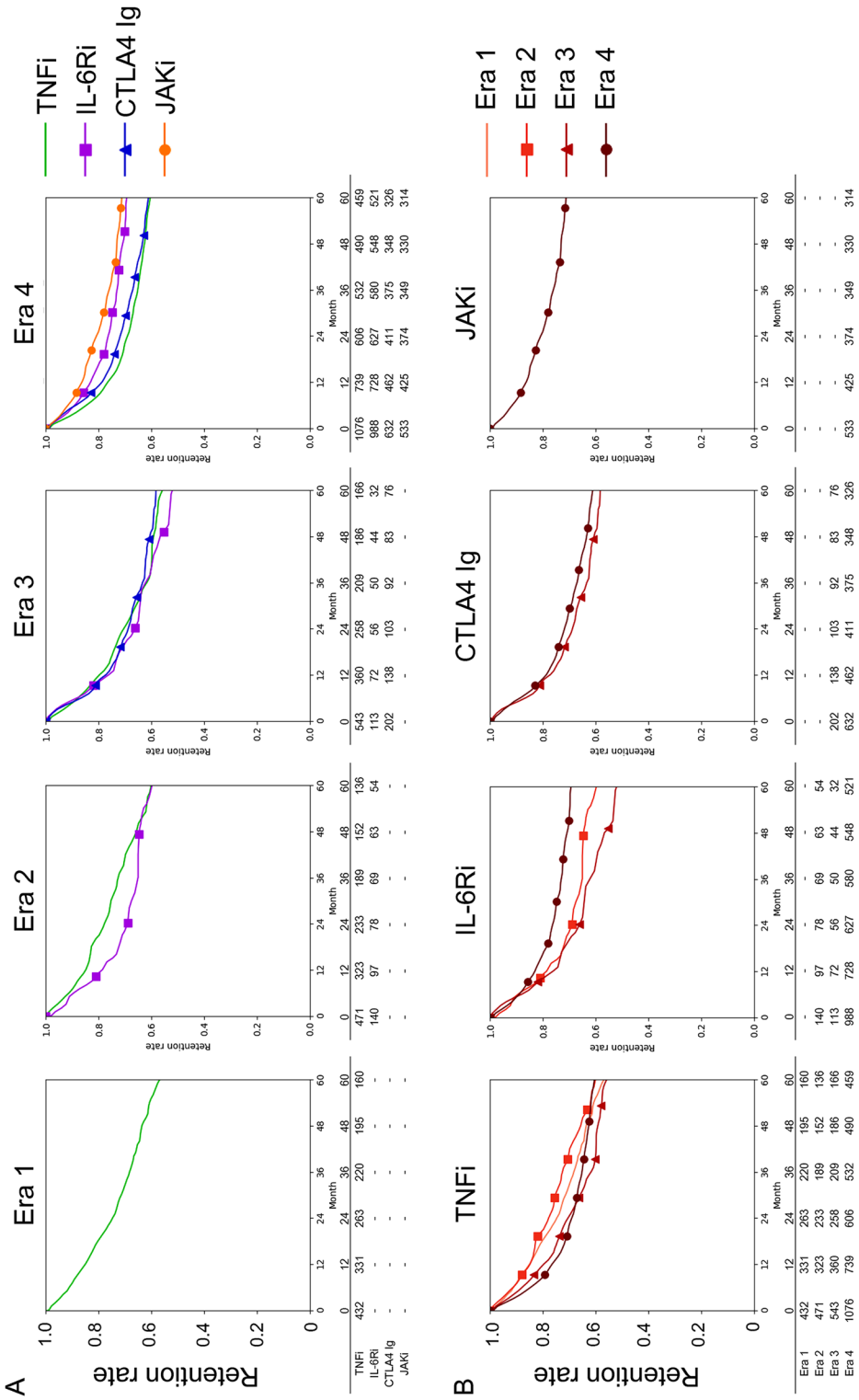


Fig. 3 Retention of b/tsDMARD-class over 5 years in four eras. Five-year retention of biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) excluding discontinuation due to remission or other reasons. **A** Retention rates of b/tsDMARDs are shown across four eras, with each graph representing a specific era and the lines showing the retention rates of different drug classes. **B** Changes in retention rates are shown for each b/tsDMARD-class across the four eras, with each graph representing a specific drug class and the lines indicating the retention rates across the different eras. *TNFi* tumor necrosis factor inhibitor, *IL-6Ri* interleukin-6 receptor inhibitor, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *JAKi* Janus kinase inhibitor. *Era 1* TNF era, *Era 2* IL-6 era, *Era 3* CTLA4 era, *Era 4* JAK era

subsequent eras, reaching the lowest rate in Era 4 (Fig. 2 and Supplementary Material Table S4). Discontinuations due to non-infectious AEs increased through Era 3 and then decreased in Era 4 (Fig. 2, Supplementary Material Tables S3 and S4). These trends suggest that while retention rates varied, improvements in management may have contributed to better outcomes in later eras. Further analysis separated the data into b/tsDMARD-naïve and with prior b/tsDMARDs groups (Supplementary Material Figs. S6 and S7). Both groups showed similar trends over time, with retention rates declining initially and then recovering in the Era 4 (JAKi era); however, this decline and subsequent recovery was more pronounced in the with prior b/tsDMARDs group. Discontinuation for all reasons excluding remission and other specified reasons was generally higher in the with prior b/tsDMARDs group compared to the naïve group, likely due to inefficacy. In the naïve group, discontinuation due to inefficacy remained relatively stable across all eras, while the with prior b/tsDMARDs group showed a notable variation across eras, with a substantial improvement in the JAKi era. These findings suggest that the with prior b/tsDMARDs group may have been more responsive to the expanding range of treatment options and evolving management practices (Supplementary Material Figures S6 and S7).

Impact of Concomitant Medications on Retention of b/tsDMARDs

The potential impact of concomitant medications on retention rates warrants attention, particularly regarding their role in infection

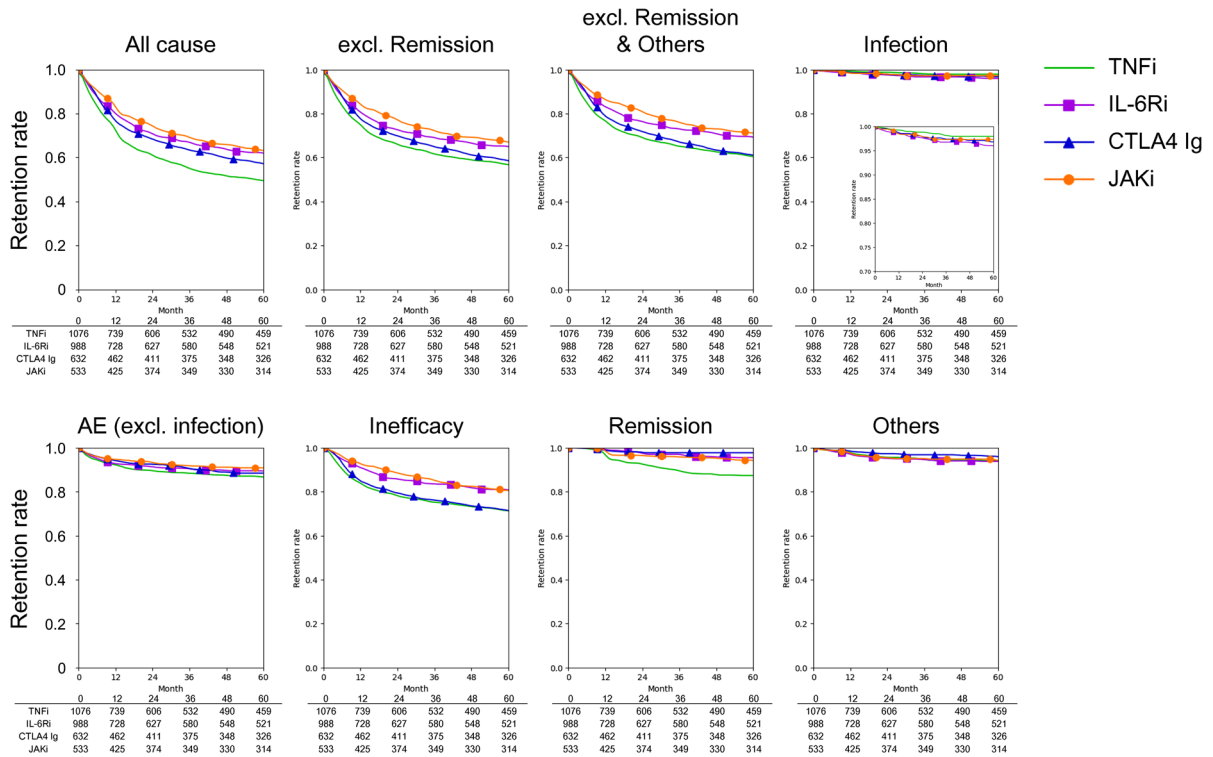
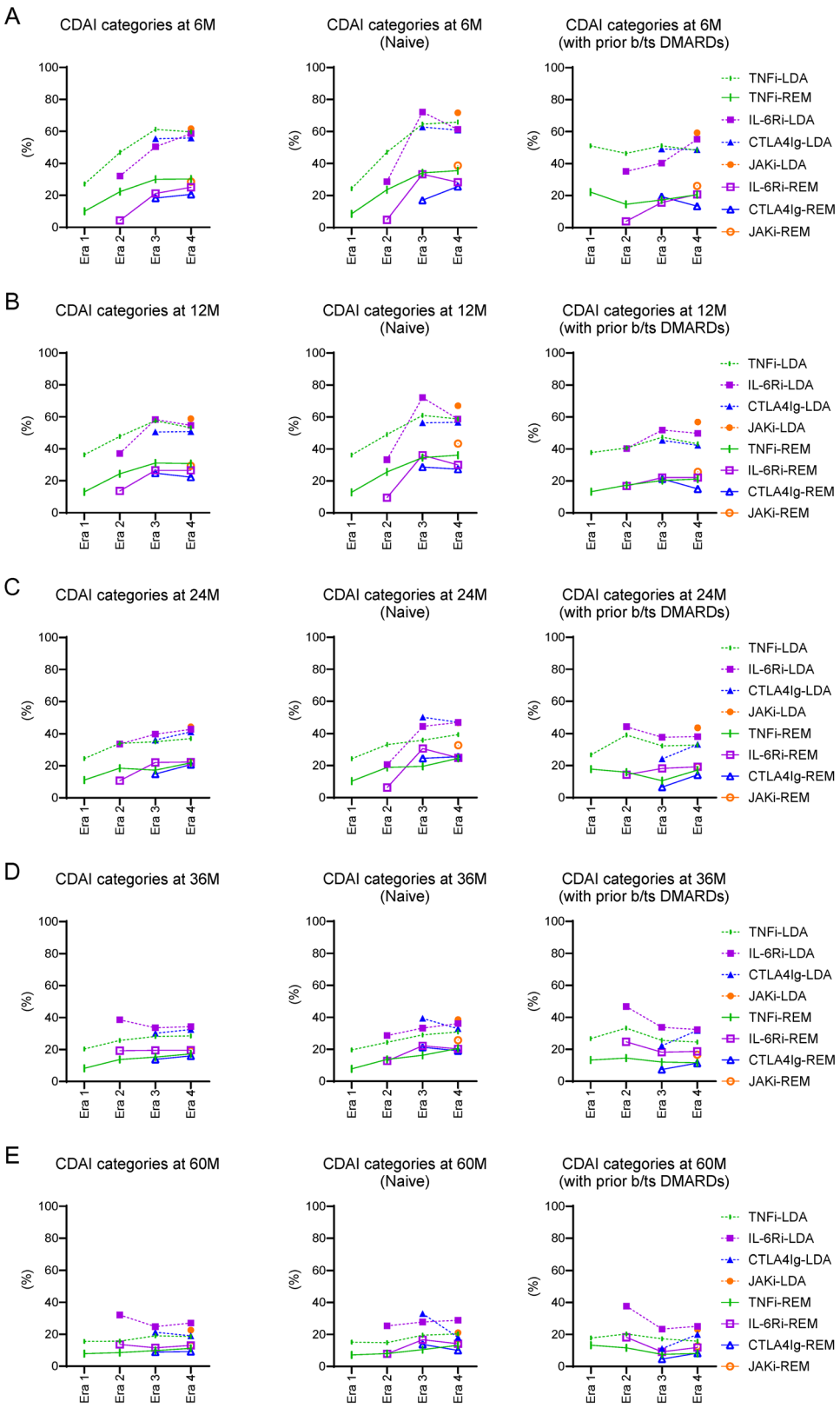


Fig. 4 Reasons for discontinuation of b/tsDMARDs in Era 4. Five-year drug retention rates representing specific discontinuation reasons in Era 4 (Janus kinase [JAK] era). *Infection* includes a nested version with the *y*-axis adjusted to [0.7–1.0] for better visualization. *Others* includes discontinuation due to socioeconomic factors, trying to conceive, self-discontinuation, patient request, comorbidities unrelated to RA, and death unrelated to RA. *AE* adverse event, *TNFi* tumor necrosis factor inhibitor, *IL-6Ri* interleukin-6 receptor inhibitor, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *JAKi* Janus kinase inhibitor


A
CDAI categories at 6M
CDAI categories at 6M (Naive)
CDAI categories at 6M (with prior b/ts DMARDs)
B
CDAI categories at 12M
CDAI categories at 12M (Naive)
CDAI categories at 12M (with prior b/ts DMARDs)
C
CDAI categories at 24M
CDAI categories at 24M (Naive)
CDAI categories at 24M (with prior b/ts DMARDs)
D
CDAI categories at 36M
CDAI categories at 36M (Naive)
CDAI categories at 36M (with prior b/ts DMARDs)
E
CDAI categories at 60M
CDAI categories at 60M (Naive)
CDAI categories at 60M (with prior b/ts DMARDs)
(%)
Era 1
Era 2
Era 3
Era 4
TNFi-LDA
TNFi-REM
IL-6Ri-LDA
CTLA4Ig-LDA
JAKi-LDA
IL-6Ri-REM
CTLA4Ig-REM
JAKi-REM

◂**Fig. 5** As-enrolled analyses of drug class efficacy across four eras. The graphs describe the treatment efficacy of different drug classes across four eras. Clinical disease activity index (CDAI) categories at **A** 6 months, **B** 12 months, **C** 24 months, **D** 36 months, and **E** 60 months are shown. *b/tsDMARDs* biologic/targeted synthetic disease-modifying antirheumatic drug, *TNFi* tumor necrosis factor inhibitor, *IL-6Ri* interleukin-6 receptor inhibitor, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *JAKi* Janus kinase inhibitor, *LDA* low disease activity, *REM* remission

risk. When the patients were stratified according to their MTX and GC use, MTX was associated with fewer infections, whereas GC was associated with more infections (Supplementary Material Figure S8A). The impact of GC was apparent in all age groups, with a greater effect in older groups (Supplementary Material Figure S8B). This underscores the importance of careful management of concomitant medications to optimize patient outcomes.

Drug-Specific Retention Rates in Era 4

Given the variability in retention rates over time, we examined drug-specific retention rates by era to gain more detailed insights (Fig. 3). In Era 3, there were no obvious differences in the retention rates, but in Era 4, the rates diverged; TNFi and CTLA4-Ig had lower retention rates among b/tsDMARDs in Era 4 (Fig. 3A). IL-6Ri and CTLA4-Ig improved the retention rates through Era 4, whereas TNFi retention rates within 2 years decreased in Era 3 and further decreased in Era 4 (Fig. 3B). These findings suggest that the retention rates of different b/tsDMARD-class have changed differently over time. To explore this further, we decided to focus our analysis on Era 4.

Differences in patient backgrounds were observed between treatments in Era 4 (Supplementary Material Table S2), including age, eGFR, disease duration, b/tsDMARD-naïve status, MTX use, GC use, and comorbidities. Specifically, TNFi was more likely to be used in younger patients with a shorter disease duration and MTX use. In contrast, CTLA4-Ig and IL-6Ri tended to be used in older patients, often without MTX. Notably, CTLA4-Ig was frequently used in patients with coexisting lung disease. JAKi were typically used as a second or later treatment in relatively younger patients (Supplementary Material Table S2). Under these treatment strategies, TNFi and CTLA4-Ig had lower retention rates in Era 4, with both frequently discontinued due to inefficacy (Fig. 4 and Supplementary Material Table S5). Of note, there were no obvious differences between b/tsDMARD-class for infection-related discontinuation.

Quality of Retention Across Drug Classes

Despite different patient backgrounds, TNFi and CTLA4-Ig showed similar retention rates and reasons for discontinuation (Fig. 4 and Supplementary Material Table S5). Thus, we next evaluated the "quality" of retention. In an as-enrolled analysis (see *"*As-enrolled analysis and per-protocol analysis in this study*"* in the method section), outcomes are measured based on the original treatment assignment, regardless of whether patients continue or discontinue treatment. In this study, any patient who discontinued or switched treatment was classified as a non-responder, regardless of the reason. All b/tsDMARD-class had similar LDA rates in the overall cohort (Fig. 5, left), in b/tsDMARD-naïve patients (Fig. 5, middle), and in patients with prior b/tsDMARDs use (Fig. 5, right). Notably, TNFi and JAKi had higher remission rates at 6 and 12 months and not inferior remission rates compared to the others at 24 months and beyond, regardless of prior b/tsDMARD us. As shown above, retention rates in the with prior b/tsDMARDs group varied significantly across eras (Supplementary Material Fig. S7), suggesting changes in treatment strategies over time; however, these adjustments did not lead to substantial improvement in retention rates for this group (Fig. 5, right).

In light of the paradoxical finding that TNFi had high remission rates (Fig. 5) but decreasing retention rates over time (Fig. 3), further investigation was conducted. Per-protocol analysis, which examines the status of patients who remain on treatment, helps to understand the "quality" of treatment. As shown in

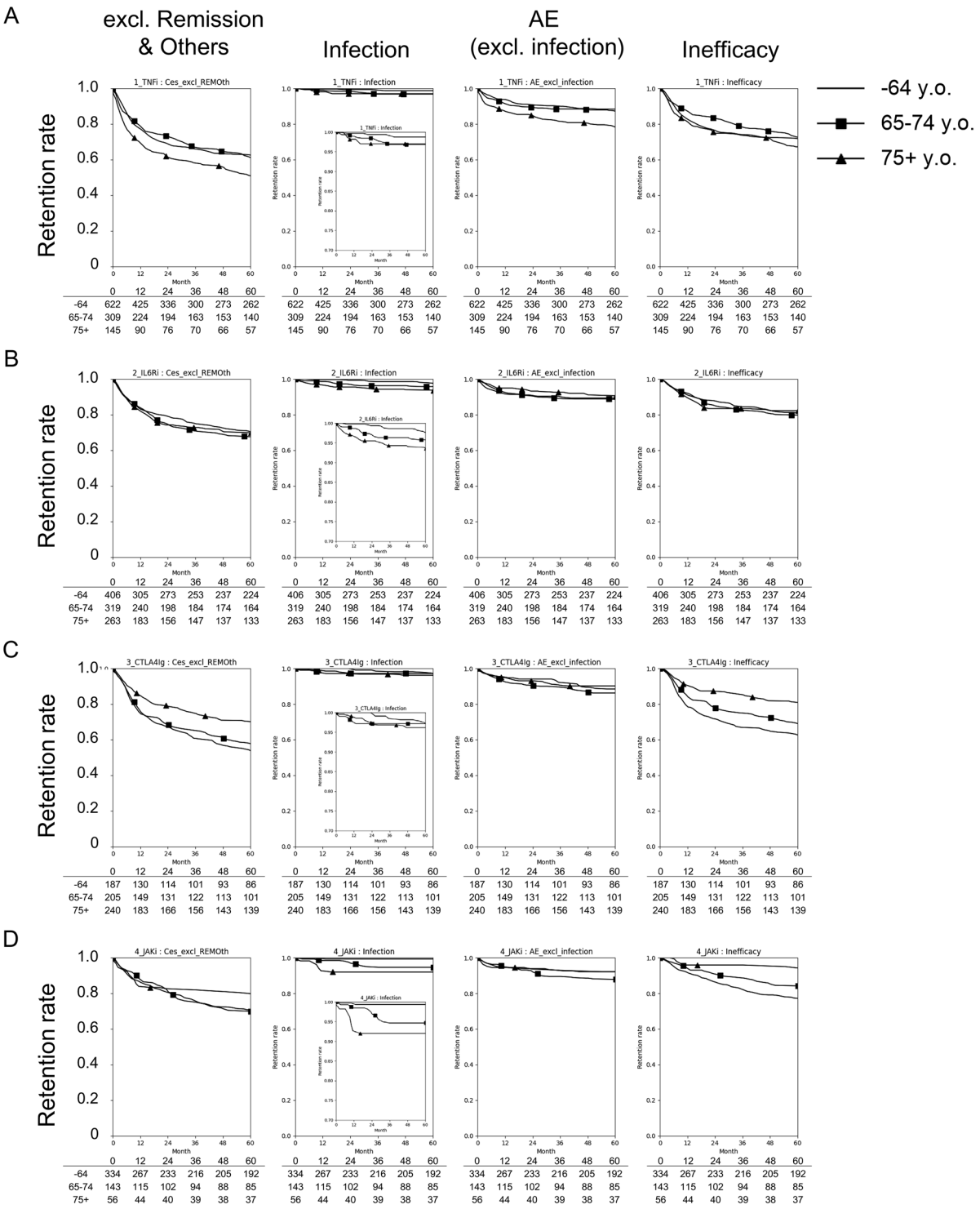


Fig. 6 Five-year drug retention by age group for b/tsDMARD-class in Era 4. Kaplan–Meier curves show 5-year drug retention rates for four biologic/targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD)-class, comparing three age groups in Era 4 (Janus kinase [JAK] era). Each panel shows the drug retention rate for **A** tumor necrosis factor inhibitors, **B** interleukin-6 receptor inhibitors, **C** cytotoxic T-lymphocyte-associated protein 4 Ig, and **D** Janus kinase inhibitors. *AE* adverse event

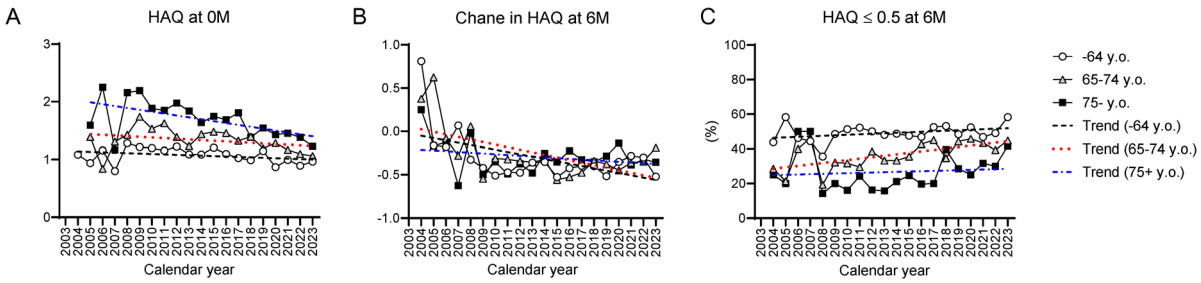


Fig. 7 Twenty-year trends in functional status of patients with rheumatoid arthritis. The graphs show changes in the health assessment questionnaire disability index (HAQ-DI) over 20 years. HAQ-DI at the time of biologic/targeted synthetic disease-modifying antirheumatic drug (b/tsDMARDs) administration (**A**), the change in HAQ-DI from 0 to 6 months (**B**), and HAQ-DI normalization (HAQ ≤ 0.5) at 6 months (**C**), categorized by three age groups with trend lines

Supplementary Material Figure S9, TNFi users were more likely to be in remission throughout the observation period (remission rate at months 6, 12, 24, 36, 60: 41.8%, 50.0%, 54.1%, 54.3%, 53.9%) compared to IL-6Ri (35.0%, 40.5%, 45.5%, 49.6%, 43.7%) and CTLA4-Ig (28.9%, 37.5%, 43.5%, 43.4%, 42.4%), which had higher retention rates than TNFi (Fig. 4). These results suggest that TNFi users continue treatment primarily for efficacy, whereas IL-6Ri and CTLA4-Ig users may continue treatment beyond efficacy, particularly in the short term.

As patient characteristics changed over time, patient age increased, and concomitant MTX use decreased accordingly (Fig. 1). Thus, we next investigated the association between MTX use, age, and b/tsDMARD-class. As shown in the as-enrolled analysis in Supplementary Material Figure S10, Senior group generally had lower rates of LDA and remission with all drugs compared to younger groups. MTX use generally resulted in higher LDA rates compared to non-MTX use, especially in Senior group (Supplementary Material Figure S10, left). TNFi had the highest or second-highest remission rate among MTX users in all age groups; however, TNFi monotherapy had the lowest remission rate compared to the other b/tsDMARD-class (Supplementary Material Figure S10, right). On the other hand, MTX use did not seem to affect the remission rate in users of IL-6Ri, CTLA4-Ig, and JAKi (Supplementary Material Figure S10, right). The relationship between age and drug retention also varied by drug class. With TNFi (Fig. 6A) and IL-6Ri (Fig. 6B), there was no obvious trend in age and discontinuation due to inefficacy. In contrast, older patients on CTLA4-Ig (Fig. 6C) and JAKi (Fig. 6D) were less likely to discontinue due to inefficacy. In summary, TNFi had a favorable remission rate but was less effective in non-MTX users and was discontinued when it was ineffective. However, a paradox was observed with CTLA4-Ig: despite lower remission rates, particularly among older patients, they continue treatment. This may suggest that factors exist that hinder the application of T2T strategies in these patients.

Functional Outcomes and HAQ Normalization

Finally, we focused on physical disability, an important outcome in RA. Over the past 20 years, HAQ-DI scores at the initiation of b/tsDMARDs showed a decreasing trend in all age groups (Fig. 7A). Although the change in HAQ-DI and HAQ-DI normalization (HAQ-DI ≤ 0.5) improved overall in all age groups during this period (Fig. 7B, C), a gap remained between Adult and Senior groups (HAQ-DI normalization rates estimated by trendline calculations: 51.9% vs. 28.5%).

DISCUSSION

The current study highlighted an increase in risk factors among patient characteristics over the past 20 years (Table 1, Fig. 1, Supplementary Material Figures S4 and S5, Table S2), while adverse events leading to discontinuation of b/tsDMARDs decreased (Fig. 2, Supplementary Material Figures S6, S7, Tables S3, and S4). Overall treatment efficacy increased for all drug classes (Fig. 5), while the treatment efficacy improved in b/tsDMARD-naïve cases and no notable improvement was observed in patients with prior b/tsDMARD experience (Fig. 5). Retention rates for IL-6Ri and CTLA4-Ig increased over time, while TNFi rates decreased (Fig. 3). However, detailed analysis revealed differences in treatment "quality" between b/tsDMARD-class (Fig. 5, Supplementary Material Figures S9 and S10), which highlighted the unmet needs; difficult-to-apply T2T patients. HAQ improvement/ normalization rates increased in all age groups, although a gap remained between younger patients and others (Fig. 7).

Statistical tests, which adjust for background factors, are valuable for providing insights to guide decision-making in cases with a wide range of treatment options. However, real-world clinical practice increasingly involves complex cases with limited treatment options, such as patients who cannot use MTX due to impaired renal function, who have substantial interstitial lung disease, or who have recurrent infections. In such cases, specific agents like abatacept are more commonly chosen. Insights from studies using statistical tests may not fully apply to these patients. Therefore, in this study, we acknowledge the limitation of not providing the defined conclusions that statistical tests may offer. Nonetheless, we performed descriptive analysis to help clinicians manage patients with significant treatment challenges.

Patient risk factors increased over the past 20 years, while the use of b/tsDMARDs accelerated around 2008 and has stabilized to date (Supplementary Material Figure S2A). Moreover, treatment was initiated earlier in patients with lower disease activity (Table 1). The increase in RA complications observed in this study may be due to two key factors: an aging population and increased use of biologics, which are likely due to the inclusion of patients with more comorbidities and higher baseline risk. Although the use of MTX has gradually decreased, the dose has remained stable since 2012 (Fig. 1). This suggests that b/tsDMARDs may be more frequently administrated to MTX-intolerant patients. Even under these circumstances, the treatment efficacy increased with decreasing AEs (Figs. 2 and 5, Supplementary Material Tables S3 and S4). Thus, the study indicates an improved management of RA.

Japan became an aged society in 1998, and the subsequent acceleration of aging has been a growing concern. To maximize the benefits of b/tsDMARDs, we have focused on improving the safety and efficacy since the early 2000s. EULAR recommends vaccination for patients with autoimmune inflammatory rheumatic diseases [17]. In Japan, the 23-valent pneumococcal polysaccharide vaccine has been approved for routine vaccination of persons aged 65 years and older since 2014, with financial support from local governments. Meanwhile, FIRST registry framework has recommended pneumococcal vaccination in patients starting b/tsDMARDs since 2008. Now, more than 80% of those aged 65 years and older in FIRST registry have been vaccinated (data not shown). PCP is a common opportunistic infection with a high mortality rate. FIRST registry framework has established guidelines for PCP prophylaxis [18], and patients receive anti-PCP drugs such as trimethoprim/sulfamethoxazole accordingly (Fig. 1, Supplementary Materials Figures S4 and S5). This initiative has significantly reduced both the incidence and mortality from PCP [18]. Although routine vaccination against influenza, SARS-CoV-2, and herpes zoster are also encouraged, these vaccination histories are not collected in FIRST registry. In general, influenza vaccination is subsidized for older adults or available at personal expense, SARS-CoV-2 was free to all ages (2021–2024), and herpes zoster is self-pay; all are voluntary in Japan. Multivariate analysis from FIRST registry previously showed that even 1 mg/day of GCs in the prednisolone equivalent increased the risk of b/tsDMARD discontinuation due to infection [19]. Similarly, this study showed that

MTX use was not associated with an increased risk of infections, whereas GC use was associated with infections leading to discontinuation of b/tsDMARDs, especially in older patients (Supplementary Material Figure S8). GCs can cause AEs, which complicate the management of RA [20, 21]. Both EULAR [4] and Japanese College of Rheumatology [2] recommend the use of GCs conditionally, advising rapid tapering and discontinuation. In contrast, the ACR recommends avoiding the use of GCs in RA [3]. FIRST registry framework has consistently promoted the non-use and early discontinuation of GCs. As a result, the rate of GC use declined sharply from 2003 to 2010 and has since stabilized at around 20% (Fig. 1, Supplementary Material Figures S4 and S5). Notably, the average dose of GCs has increased slightly since 2013. This may reflect a shift in the purpose of GC use from controlling arthritis to managing RA-related extra-articular complications. Unfortunately, because FIRST registry does not have comprehensive data on concomitant medication use until 2020, we cannot discuss GC tapering trends during b/tsDMARD treatment in this study. In combination with the initiatives already discussed, FIRST registry framework includes plain CT in addition to regular screening prior to b/tsDMARD administration. This strategy was effective in detecting various comorbidities, including malignancies, which likely contributed to improved patient survival [12]. CT scans also identified asymptomatic infections such as non-tuberculous mycobacteria, aspergillosis, cryptococcosis, panbronchiolitis, tuberculosis, and chronic sinusitis [12, 22]. Because these conditions could potentially worsen with b/tsDMARD treatment, patients received appropriate evaluation, treatment, or follow-up as needed [12, 22]. The incidence of infections over time has shown variability across studies [23–25]; however, this study demonstrated a reduction in serious infections, including opportunistic infections. These comprehensive efforts likely contributed to the decrease in infection rates over time observed in this study, despite the increasing age and comorbidities of the patient population.

Numerous studies with statistical techniques have shown that TNFi have a lower retention rate compared to non-TNFi and JAKi [26–32]. Similarly, TNFi retention rates declined over eras, showing the lowest among b/tsDMARDs in Era 4 (Fig. 3). However, this study illustrated that the efficacy of TNFi improved over time, resulting in the highest remission rate in Era 4, although it was primarily discontinued due to inefficacy (Figs. 4, 5 and Supplementary Material Figure S9). Although TNFi retention rates are reportedly low in elderly patients, those using MTX with TNFi showed efficacy comparable to other b/tsDMARDs (Supplementary Material Figure S10). Thus, the younger age in the TNFi group does not explain the higher remission rates achieved with TNFi in this study. Concurrently, these data suggest that despite good efficacy, TNFi was discontinued when deemed ineffective. More importantly, the study highlighted that patients on IL-6Ri and CTLA4-Ig were more likely to remain on the treatment with a lower remission rate (Supplementary Material Figure S9). Differences in patient background (Supplementary Material Table S2) naturally affect outcomes; however, the key point is that certain population face challenges in applying T2T. TNFi was often used as the first b/tsDMARD, which may lead to early discontinuation to adhere to T2T strategies. In contrast, IL-6Ri and CTLA4-Ig were more likely to be administered to patients who were older, had a lower eGFR, and thus received less concomitant MTX. Furthermore, patients who received CTLA4-Ig appeared to have a higher risk of infection. These factors may prevent a switching from IL-6Ri or CTLA4-Ig to other drugs, such as TNFi (MTX is critical for efficacy) or JAKi (safety concerns in elderly patients [16]). However, it is important to note that the association between RA inflammation and eGFR decline [33, 34]. Although hypothetical, if patients and rheumatologists hesitate to escalate treatment because of the age, it could prolong inflammation, leading to lower eGFR, limiting MTX use, fewer b/tsDMARD options, and ultimately worse outcomes. In summary, Era 4 highlighted differences in drug retention rates, with TNFi discontinuation due to inefficacy being particularly prominent. TNFi is often switched when deemed ineffective, which may explain the lower retention rates observed in previous studies. However, given

the abundant evidence of TNFi, it is worth noting that retention rates should not be the sole factor in treatment decisions. Additionally, an unmet medical need is identified: some patients continue treatment without achieving remission, suggesting that patient background may complicate T2T strategy implementation.

Functional impairment in patients with RA may not have improved over time [35, 36]. Disability-adjusted life years (DALYs) measure years of life lost (YLL) due to premature mortality and years lived with disability (YLD), reflecting the total disease burden. Age-adjusted DALYs have improved in the general population [37], whereas for patients with RA, they have worsened or remained stable [8, 38]. Considering that mortality rates among patients with RA have globally decreased over time [1, 8, 39, 40], a decrease in YLL and an increase in YLD is suggested. YLD in RA consists of comorbidities, complications, and functional impairment caused by uncontrolled RA. This study showed that discontinuation due to AEs, and "other reasons" decreased over time (Supplementary Material Table S4), suggesting that disability associated with treatment-related comorbidities and complications has decreased. However, improving functional impairment from RA inflammation is crucial to closing the DALY gap; as this aspect remains an unmet need, as highlighted by reports [36, 41, 42], and this study. While our study showed a marginal improvement in the rate of HAQ normalization, gaps remain between younger and older patients (Fig. 7). Considering that more than 75% of the general population under 75 years of age have an HAQ score of 0.38 or less [43], advances in RA management could help alleviate these challenges. Integrating these findings with the earlier discussions highlights the importance of a comprehensive approach.

Possible approaches to the issues raised in this study include: (i) considering the patients remain on treatment despite only achieving LDA, and lower response rates in patients with prior b/tsDMARD, there is a continued need for new drug development, (ii) we have recently reported factors associated with failure to achieve HAQ normalization [44]. Early and aggressive intervention should be considered in such patients, (iii) delay in treatment can cause irreversible functional impairment. Precision medicine is needed to avoid missing the window of opportunity [14], (iv) recent evidence suggests that T2T may not improve physical function alone [45]. Therefore, a multifaceted management approach is needed. Potential strategies include management of comorbidities such as depression and fibromyalgia [46, 47]; implementation of resistance training [48–50]; dietary therapy [50]; enhancement of self-efficacy [51, 52]; (v) management of osteoporosis [53], as fractures can lead to physical disability, especially given the low treatment rates [54]. These comprehensive approaches will be essential for effective RA management.

This study includes certain limitations. While this study confirmed unmet needs reported worldwide, whereas the findings may not be directly applicable to global populations. Furthermore, potential biases in patient selection must be considered when interpreting the results. Additionally, this descriptive analysis does not establish causation. The observed reduction in AEs could be due to people being biologically "younger" today. However, it is clear that older patients still experience greater physical disability. The structure of the Japanese healthcare system, which allows patients to be treated at multiple hospitals, can lead to data gaps if follow-up visits are missed. This issue is particularly important for deceased patients, as FIRST registry can only capture deaths that occur at participating sites. For patients who discontinue visits, it is not possible to distinguish between patient-initiated discontinuation and death, resulting in incomplete mortality data and preventing this study from analyzing mortality outcomes. Nevertheless, as discussed in this paper, numerous studies have documented a decrease in mortality in patients with RA.

CONCLUSIONS

As the population continues to age, more effective management strategies that balance safety are warranted. The development of new drugs and the comprehensive management including non-drug interventions will be possible approaches.

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Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Koshiro Sonomoto has received speaking fees from AbbVie, Eli Lilly Japan, Gilead Sciences, GlaxoSmithKline, Janssen, Pfizer Japan, UCB Japan, Astellas, Ayumi, Chugai, Taisho, Tanabe Mitsubishi and has received research funding from UCB Japan. Shingo Nakayamada has received consulting fees, speaking fees, lecture fees, and/or honoraria from AstraZeneca, GlaxoSmithKline, Pfizer, Bristol-Myers, Astellas, Asahi-kasei, AbbVie, Chugai, Sanofi, Eisai, Gilead Sciences, Mitsubishi-Tanabe, Janssen, Eli Lilly, and Ayumi. Yoshiya Tanaka has received speaking fees and/or honoraria from Eli Lilly, AstraZeneca, AbbVie, Gilead, Chugai, Behringer-Ingelheim, GlaxoSmithKline, Eisai, Taisho, Bristol-Myers, Pfizer, Taiho, received research grants from Mitsubishi-Tanabe, Eisai, Chugai, Taisho. Yoshiya Tanaka is an Editorial Board member of Rheumatology and Therapy. Yoshiya Tanaka was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Hiroaki Tanaka and Atsushi Nagayasu have nothing to disclose.

Ethical Approval. This study followed the Declaration of Helsinki and was approved by the Ethics Committee of the University of Occupational and Environmental Health School of Medicine (#UOEHCRB21-068). Informed consent was obtained from all participants based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese Ministry of Health, Labor and Welfare. Written informed consent was obtained from participants enrolled after April 2015, and written or verbal consent was obtained from others.

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