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Therapeutic Trajectories, Drug Survival, and Adverse Events in Patients with Difficult-to-Treat Rheumatoid Arthritis in Real-World Clinical Practice

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Abstract

Background/Objectives: Difficult-to-treat rheumatoid arthritis (D2T-RA) affects approximately 11.7% of patients. Real-world data on treatment trajectories, biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), and adverse events (AEs) remain limited. This study evaluated treatment patterns, line survival, and AEs in D2T-RA. **Methods**: This retrospective study included 97 D2T-RA patients. Treatment-line survival was assessed using Kaplan–Meier analysis with log-rank tests and a cluster-robust Cox proportional hazards model. Generalized estimating equation models (GEE) identified factors associated with AEs. Cluster analysis (K-modes, MCA followed by K-means, and hierarchical clustering) was performed to identify treatment patterns. **Results**: A median time to first prescription of b/tsDMARDs was 1369 days (IQR 852–2557). Inefficacy was the most common reason for switching (65.8%); csDMARD/GCs were discontinued for inefficacy more frequently than b/tsDMARD (70.1% vs. 61.3%). Among 470 b/tsDMARD-containing treatment lines, interleukin-6 (IL-6) inhibitors were most common (127 lines, 27.0%), followed by tumor necrosis factor-α (TNF-α) inhibitors (109 lines, 23.2%), Janus kinase (JAK) inhibitors (89 lines, 18.9%), rituximab (82 lines, 17.4%), and abatacept (61 lines, 13.0%). The agents used included tocilizumab, levilimab, sarilumab, and olokizumab; adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol; and tofacitinib, baricitinib, and upadacitinib. In adjusted GEE models, treatment type was not a significant predictor of AE occurrence (OR 0.93, 95% CI 0.63–1.36); line number and female sex were independently associated with AEs, and a previous AE increased the risk of AE on the current line (OR 1.72, 95% CI 1.13–2.60; $p = 0.011$). TNF-α inhibitors were prescribed without concomitant methotrexate in 59 of 109 treatment lines (54.1%). At the final treatment line, lower disease activity was observed with abatacept, levilimab, and olokizumab, whereas higher values were observed with rituximab and etanercept; between-treatment differences were significant for DAS28-ESR ($p = 0.0269$), but not for CDAI, SDAI, or DAS28-CRP. Cluster analysis identified three exploratory treatment patterns, differing primarily in the use of tsDMARDs and hydroxychloroquine. **Conclusions**: D2T-RA is characterized by multiple treatment lines and frequent switching due to inefficacy, particularly for csDMARD/GC therapy. Among the targeted therapies evaluated, IL-6 inhibitors and abatacept were associated with

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lower disease activity at the final treatment line, whereas rituximab and etanercept were associated with higher values; these exploratory observations do not establish comparative effectiveness. The frequent use of TNF-α inhibitors without concomitant methotrexate highlights a potential target for treatment optimization. A history of AEs may help identify patients requiring closer safety monitoring.

Keywords: rheumatoid arthritis; D2T-RA; treatment lines; adverse events; methotrexate; csDMARDs; biologic DMARDs; JAK inhibitors; cluster analysis

1. Introduction

Difficult-to-treat rheumatoid arthritis (D2T-RA) represents a clinically significant subgroup of patients with rheumatoid arthritis (RA) who continue to experience persistent disease activity or symptoms despite adequate therapy. According to the EULAR definition, D2T-RA includes patients with failure of at least two biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) with different mechanisms of action, in the presence of signs of active or progressive disease and the perception of disease management as problematic by either the physician or the patient [1].

According to a meta-analysis including 23 studies (27,897 patients from 13 countries), approximately 11.7% of patients with RA meet the criteria for D2T-RA (95% CI: 9.5–14.3%) [2]. The prevalence decreases with stricter definitions: 4.3% (2.7–6.7%) for failure of three or more b/tsDMARDs and 1.6% (0.6–4.3%) for failure of four or more agents. D2T-RA is considered a heterogeneous condition in which multiple factors, including comorbidities, low socioeconomic status, altered pain perception, and specific synovial cellular composition, may contribute to persistent symptoms [3].

The current treatment strategy for RA is based on the treat-to-target principle, which involves early initiation of conventional synthetic DMARD (csDMARD) therapy followed by treatment escalation until remission or low disease activity is achieved [4]. Methotrexate (MTX), in combination with short-term glucocorticoids (GCs), is recommended as first-line therapy, with subsequent addition of biologic or targeted agents in the absence of an adequate response within 3–6 months. In cases of failure of the first b/tsDMARD, switching therapy is recommended; however, after failure of a tumor necrosis factor-α (TNF-α) or interleukin-6 (IL-6) inhibitor, the use of a second agent from the same class is also acceptable [4]. Chatzidionysiou et al. demonstrated that after failure of a first biologic agent (abatacept, rituximab, or tocilizumab), switching to a TNF-α inhibitor resulted in low disease activity or remission in 40% of patients after 6 months [5]. Kanda et al. showed that among patients with RA (n = 687) who failed first-line b/tsDMARD therapy, second-line JAK inhibitors were associated with the highest remission rates at 24 weeks compared with TNF-α inhibitors, IL-6 inhibitors, and abatacept. Among JAK inhibitors, upadacitinib demonstrated the best outcomes [6]. Most biologic agents are recommended in combination with csDMARDs (primarily MTX), whereas IL-6 inhibitors and JAK inhibitors may be used as monotherapy in cases of csDMARD intolerance (including leflunomide [LEF] and sulfasalazine [SSZ]) [4].

Despite the availability of international standardized clinical guidelines, substantial variability in therapeutic strategies persists in real-world practice. One possible explanation is the relatively recent formalization of the D2T-RA concept in the 2020 EULAR recommendations [1], which continue to evolve [4]. Inefficacy remains the most common reason for switching b/tsDMARDs, and the switching rate within 12 months ranges from 24% to 32%, according to a study involving 2839 patients with RA. The best second-line

drug survival was observed for tocilizumab, rituximab, and tofacitinib [7]. Another study involving 6040 patients demonstrated that treatment switching was primarily driven by inadequate response (43.3%), loss of efficacy (25.8%), and non-allergic adverse events (AEs) (13.7%) [8]. Younger age, female sex, and smoking were associated with refractoriness, whereas standard clinical RA factors failed to predict therapeutic response [8]. Similar risk factors had been proposed previously, with the addition of obesity and high social deprivation. The median time to development of refractory disease (defined as failure of a third biologic class) was 8 years, reflecting the prolonged and complex treatment trajectory of this patient population [9]. In addition, the median duration of the first b/tsDMARD treatment line decreased from 208 days in 2015–2017 to 153 days in 2018–2021 ($p < 0.001$) [10]. This may reflect both changes in clinical approaches and increased availability of novel therapies. However, among patients with four or more treatment switches, 85.3% returned to a previously used drug class [10].

Thus, the formation of real-world therapeutic trajectories in patients with D2T-RA, the duration of treatment lines, the structure of switching reasons, and the profile of AEs remain insufficiently studied.

2. Materials and Methods

2.1. Study Design and Participants

This study used data from the Moscow City Registry of Patients with Rheumatic Diseases, combining records from three interdistrict rheumatology centers. At the time of analysis, the registry contained 54,967 patients, of whom 2405 were receiving bDMARDs or tsDMARDs; the remainder were on csDMARDs.

An extended evaluation protocol was completed by 315 of 17,276 patients, who were consecutively assigned to one of three groups until the planned sample size of 105 patients per group was reached:

Group 1: RA with disease control on csDMARDs ($n = 105$);
Group 2: RA with disease control on bDMARDs or tsDMARDs, not meeting D2T-RA criteria ($n = 105$);
Group 3: patients meeting D2T-RA criteria ($n = 105$).

Consecutive enrolment continued until the target sample size was reached in each group. Written informed consent was obtained from all participants.

For the analysis of treatment lines and clustering of treatment patterns, data from 97 patients in Group 3 were used; 8 patients were excluded due to incomplete documentation.

Eligible participants were men and women aged 18 years or older who fulfilled the 2010 ACR/EULAR classification criteria for RA and national clinical practice guidelines. Both seropositive and seronegative RA patients were included, provided that comorbid conditions did not require hospitalization in specialized inpatient departments.

Patients were excluded if they had seropositive RA complicated by Felty syndrome (M05.0), rheumatoid lung disease (M05.1), rheumatoid vasculitis (M05.2), or unspecified seropositive RA (M05.9), or other forms of RA classified under ICD-10 code M06, including adult-onset Still's disease (M06.1), rheumatoid bursitis (M06.2), rheumatoid nodules (M06.3), inflammatory polyarthropathy (M06.4), other specified rheumatoid arthritis (M06.8), or unspecified rheumatoid arthritis (M06.9). Additional exclusion criteria comprised comorbid conditions expected to substantially affect life expectancy, including terminal malignancy, New York Heart Association class IV heart failure, decompensated diabetes mellitus, end-stage renal disease, liver cirrhosis with a Child–Pugh score ≥ 10, HIV infection, active hepatitis B or C (positive antibody titers with detectable viral load), and active tuberculosis of any localization. Patients with other immune-mediated inflam-

matory rheumatic diseases or autoimmune disorders were excluded, as were those with any clinically significant condition that could interfere with study participation or data interpretation, including substance abuse, organic psychiatric disorders, or severe organ dysfunction. Pregnant and lactating women were also excluded.

2.2. Clinical and Laboratory Assessments

Data were extracted from electronic medical records and paper charts. Patient characteristics recorded included age, sex, disability status, functional class, educational level, seropositivity for rheumatoid factor and anti-citrullinated protein antibodies, disease activity indices (DAS28-CRP, DAS28-ESR, CDAI, SDAI), erythrocyte sedimentation rate, and C-reactive protein levels. The follow-up period was calculated from the date of first recorded RA therapy to the last documented visit.

The diagnosis of D2T-RA was confirmed according to the EULAR definition (2020/2021 criteria), which requires: (1) failure of at least two b/tsDMARDs with different mechanisms of action; (2) presence of at least one of five sub-criteria indicating active or progressive disease (including moderate/high disease activity, rapid radiographic progression, persistent symptoms despite treatment, inability to reduce glucocorticoid dose, or rapid progression of functional impairment); and (3) perception of disease management as problematic by either the physician or the patient.

In the study database, these criteria were operationalized using dedicated variables: criteria_dt2ra_1 (failure of $\geq$2 b/tsDMARDs) was met by 100% of patients (97/97); criteria_dt2ra_2 (active/progressive disease, $\geq$1 of 5 sub-criteria) by 100% (97/97); and criteria_dt2ra_3 (problematic disease management) by 94/97 (96.9%): in 87 cases by both patient report and physician assessment, and in 7 cases by patient report only. Overall, 94/97 (96.9%) formally met all EULAR criteria; the remaining three did not meet criterion 3, and one was in DAS28-CRP remission (1.27) at assessment. Comorbidity burden was assessed using the Charlson Comorbidity Index (CCI), calculated based on documented comorbidities at the time of study inclusion; its components (myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, chronic obstructive pulmonary disease, and peptic ulcer disease) were recorded for supplementary analysis.

2.3. Extended Clinical Evaluation

All patients underwent a comprehensive clinical evaluation, including collection of medical history, physical examination, and joint assessment. Cardiovascular risk was evaluated using the SCORE-2 and SCORE2-OP scales. Comorbidity burden was further characterized using the Rheumatic Disease Comorbidity Index (RDCI).

Laboratory investigations included complete blood count, urinalysis, biochemical blood analysis, lipid profile, and standard coagulation tests. Immunological assessments included rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), antinuclear antibodies (ANA), and immunoblot for ANA when indicated. Methotrexate concentration in blood was measured using high-performance liquid chromatography. Cellular and humoral immunity were assessed, and proteomic analysis was performed using mass spectrometry.

Instrumental examinations included radiography of the hands and feet, ultrasound or MRI of joints when clinically indicated, ultrasound Doppler scanning of the neck vessels, echocardiography, and high-resolution computed tomography of the chest. Respiratory function was evaluated using spirometry and body plethysmography. Consultations with specialists were performed as indicated, including psychotherapist/psychiatrist, pulmonologist (for RA-associated interstitial lung disease), and other specialists when necessary.

Patient-reported outcomes were assessed using validated instruments: the Beliefs about Medicines Questionnaire (BMQ) short form, the Compliance Questionnaire for Rheumatology (CQR-5), and the Quantitative Adherence Assessment (QAA-25). Functional disability was evaluated using the Health Assessment Questionnaire (HAQ). Quality of life and health status were assessed using the EQ-5D-3L, the Patient Health Questionnaire-9 (PHQ-9), and the SF-36. Psychosocial and neurological status were evaluated using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), the Fibromyalgia Rapid Screening Tool (FiRST-2010), the Generalized Anxiety Disorder-7 (GAD-7), the Personality Inventory for DSM-5 (PID-5), the Mini International Neuropsychiatric Interview (MINI), the Hospital Anxiety and Depression Scale (HADS) for patients with suspected fibromyalgia or neuropathic pain, and the painDETECT questionnaire for central sensitization assessment.

2.4. Treatment Lines and Drug Classification

A treatment line was defined as any distinct combination of drugs prescribed to a patient, based on the presence of GCs, csDMARDs, bDMARDs, or JAK inhibitors. A treatment line represents a period of continuous drug exposure, not merely a prescription record. A new line was recorded whenever there was any change in the drug combination, including addition, discontinuation, or replacement of any medication. Dose adjustments alone were not considered new treatment lines. Consecutive records with the same drug combination were merged into a single treatment line, with the duration calculated from the start of the first record to the end of the last record.

Example. Patient X had the following records: MTX 15 mg (01.2018–05.2018); MTX 20 mg (05.2018–09.2018); MTX 20 mg + LEF 10 mg (09.2018–02.2020); HCQ + GCs + MTX + baricitinib (02.2020–11.2020). Because dose changes do not start a new line, the first two records form a single line "MTX" (01.2018–09.2018). The third record starts a new line "MTX + LEF" (09.2018–02.2020). Both of these lines are classified as csDMARD lines. The fourth record starts a new line "HCQ + GCs + MTX + baricitinib" (02.2020–11.2020), which is automatically classified as a bDMARD/targeted line, specifically a JAK inhibitor line, because the presence of any bDMARD or JAK inhibitor determines the line category, regardless of concomitant csDMARDs and GCs.

Drugs were categorized as follows: GCs, csDMARDs including MTX, LEF, SSZ, HCQ, AZA, gold salts (GOLD); bDMARDs including TNF-α inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol), IL-6 inhibitors (tocilizumab, levilimab, sarilumab, olokizumab, sirukumab), B-cell inhibitors (rituximab), T-cell inhibitors (abatacept), GM-CSF inhibitors (otilimab), and IL-17A inhibitors (netakimab); and JAK inhibitors (tofacitinib, baricitinib, upadacitinib).

For the purposes of this analysis, treatment lines were classified into two mutually exclusive categories: non-biologic therapy and biologic/targeted therapy. Non-biologic therapy included all lines without bDMARDs or JAK inhibitors—that is, csDMARD-based regimens (with or without concomitant GCs) and GCs monotherapy. This binary classification reflects the clinical distinction between non-biologic and biologic/targeted treatment phases and was used to identify patients who had not yet received targeted therapy. GCs monotherapy was retained within the non-biologic category because, although GCs are not disease-modifying agents, such periods represented intervals without disease-modifying treatment rather than a distinct therapeutic strategy. GCs monotherapy occurred in 19.6% of patients (19 of 97), most of whom (16 of 19) had a single such episode; these were typically short-term bridging or symptomatic intervals between disease-modifying therapies.

For each treatment line, the reason for discontinuation was extracted from the last record of the line (latest date), while the occurrence of any AE during the line was recorded

if at least one record within the line documented an AE. Records with a documented end date preceding the start date were excluded as technical data-entry errors. Return after discontinuation was defined at the patient level as resumption of the same drug after at least one documented discontinuation.

2.5. Reasons for Treatment Switching

Reasons for discontinuation or switching of therapy were classified according to the primary documented reason in the medical records into the following categories: inefficacy (after 3 months), AEs, combined inefficacy and AEs, technical impossibility (financial reasons, lack of drug registration or supply), discontinuation or interruption for other reasons, achievement of low disease activity, achievement of remission, infectious events, and unspecified. Each switch was assigned a single primary reason, except for the combined category, which was used when both inefficacy and AEs were documented as contributing to the decision.

AEs were classified into the following categories: gastrointestinal (dyspepsia, nausea/vomiting, diarrhoea, aphthous stomatitis, abdominal pain); dermatological (urticaria, rash, dermatitis, pruritus, hair loss); hepatological (transaminase elevation >3× upper limit of normal); haematological (thrombocytopenia, leukopenia); infectious (herpesvirus infection, respiratory and urinary tract infections, and other infectious events); cardiovascular (hypertensive crisis); neurological (headache, dizziness, polyneuropathy); ophthalmological (eye discomfort, visual impairment); respiratory (dyspnoea); gynaecological (uterine bleeding); allergic (allergic reaction, angioedema, post-injection dyspnoea); infusion-related (local or infusion reactions); and other.

A recurrent AE was defined as the occurrence of an AE on a subsequent treatment line after an AE had been documented on the preceding line.

Statistical Analysis of AEs

AE analyses were performed at two levels: per treatment line and per event. The denominator for per-line analyses was the total number of treatment lines (n = 866). The denominator for per-patient analyses was the total number of patients in the D2T-RA cohort (n = 97). Frequencies of individual AE types were calculated as a proportion of all documented pharmacotherapy records (n = 1029).

For per-line analyses, Generalized Estimating Equations (GEE) with a binomial family and an exchangeable working correlation structure were used, with patient as the clustering unit to account for within-patient correlation across repeated treatment lines. The primary model assessed the association between treatment type (bDMARD/JAK vs. csDMARD/GCs) and AE occurrence, adjusted for age, sex, line number, and CCI. Treatment duration was initially included as a covariate but was removed from the final model because it is a mediator rather than a confounder: it lies on the causal pathway between treatment type and AE occurrence, and adjusting for it could introduce collider bias. An additional model assessed the association between the presence of an AE on the previous treatment line and AE occurrence on the current line, using the same covariates. Adjusted ORs with 95% confidence intervals were reported.

For per-event analyses, the first treatment line with a documented AE was defined as the index event. All subsequent treatment lines were included as individual observations, each coded as 1 if an AE was documented and 0 otherwise. The association between the treatment class of the index event and recurrent AEs was assessed using GEE with patient as the clustering unit, adjusted for line number, age, sex, CCI, and the treatment class on which the index AE occurred.

Exposure-adjusted AE incidence rates were calculated as the number of AEs per 100 patient-years of follow-up, with patient-years computed as the sum of line durations divided by 365.25. Incidence rate ratios (IRR) were estimated using Poisson regression with a log-offset for exposure time.

2.6. Clustering of Treatment Patterns

To identify treatment patterns, each patient was represented as a binary vector across nine drug classes (MTX, bDMARDs, LEF, SSZ, JAK inhibitors, HCQ, AZA, GOLD, and GCs), where 1 indicated any recorded exposure to the class and 0 indicated no exposure.

Four clustering approaches appropriate for binary data were applied:

1. K-modes, a partitional algorithm analogous to k-means but using Hamming distance and modes instead of means. Solutions were computed for k = 2 to 6 with 10 random initializations (init = "Huang", n_init = 10).
2. Multiple correspondence analysis (MCA) followed by k-means. MCA was performed with 4 components; k-means was applied with 20 initializations for k = 2 to 6.
3. Hierarchical clustering with Gower distance (average linkage), a metric that handles binary and mixed data types.
4. Hierarchical clustering with Dice distance (average linkage).

For hierarchical methods, dendrograms were cut at multiple thresholds (0.2–0.5 for Gower and 0.3–0.7 for Dice) to assess sensitivity. For partitional methods (K-modes, k-means), the number of clusters was chosen by visual inspection of the silhouette score, cluster sizes, and clinical interpretability.

Cluster stability was assessed by bootstrap resampling (n = 300 iterations) with the Jaccard stability index, defined as the proportion of bootstrap iterations in which a given pair of patients was assigned to the same cluster. A cluster was considered stable if the mean pairwise stability exceeded 0.75.

K-modes was selected as the primary clustering method because it is specifically designed for binary data and does not require distance-based assumptions. MCA followed by K-means was applied as a confirmatory approach, and hierarchical methods (Gower and Dice distance) were used as sensitivity analyses to assess whether the observed pattern was robust to the choice of algorithm.

Cluster profiles were summarized as the proportion of patients within each cluster receiving each drug class. All analyses were performed in Python version 3.14.2 using scikit-learn, scipy, kmodes, prince, and gower.

2.7. Statistical Analysis

Statistical analyses were performed using Python version 3.14.2 with the following libraries: pandas (version 2.3.3; data manipulation), lifelines (version 0.30.3; survival analysis), scipy (version 1.17.0; statistical tests), and statsmodels (version 0.14.6; regression models). Descriptive statistics are presented as medians with interquartile ranges (IQRs) for continuous variables and frequencies with percentages for categorical variables. Treatment-line survival was assessed using Kaplan–Meier analysis. Each treatment line was treated as a separate observation, with censoring at the start of the subsequent treatment line or at the patient's last documented visit, whichever came first. Kaplan–Meier curves are presented for descriptive purposes only, and log-rank p-values are reported as descriptive comparisons rather than formal hypothesis tests, because treatment lines within a patient are not independent observations. To account for within-patient correlation across repeated treatment lines, a cluster-robust Cox proportional hazards model was fitted with patient as the clustering unit, adjusted for treatment type, line number, age, sex, and Charlson comorbidity index. The Kruskal–Wallis test was used to compare disease activity indices

across different drug groups at the final treatment line. All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant.

3. Results

The mean age of patients was 57.51 ± 11.13 years; 87.6% were women, 78.35% had third-degree disability status, and 61.86% had higher education. All patients received bDMARDs and/or JAK inhibitors. The initial dataset included 1029 unique pharmacotherapy records. To ensure correct matching of treatment lines, drug names were standardized and technical input errors were removed. In subsequent analyses, records containing the same drugs but different dosages were merged into a single treatment line (with correspondingly increased treatment duration).

3.1. Treatment Characteristics and Time to Targeted Therapy Initiation

Patient therapy was evaluated for compliance with the 2025 EULAR recommendations for RA [4]. All patients received MTX at some point during their treatment history (consistent with the recommendations): 46 as monotherapy and 51 in combination therapy (most commonly with GCs, 16 cases). Overall, 78 patients received GCs (80.4%) with a median duration of use of 1205 days. The median time from initiation of first-line therapy to the first prescription of a bDMARD or JAK inhibitor was 1369 days (IQR 852–2557), or 3.7 years (Figure 1). Only 2.1% of patients received targeted therapy within 3 months after MTX initiation, and 4.1% within 6 months.

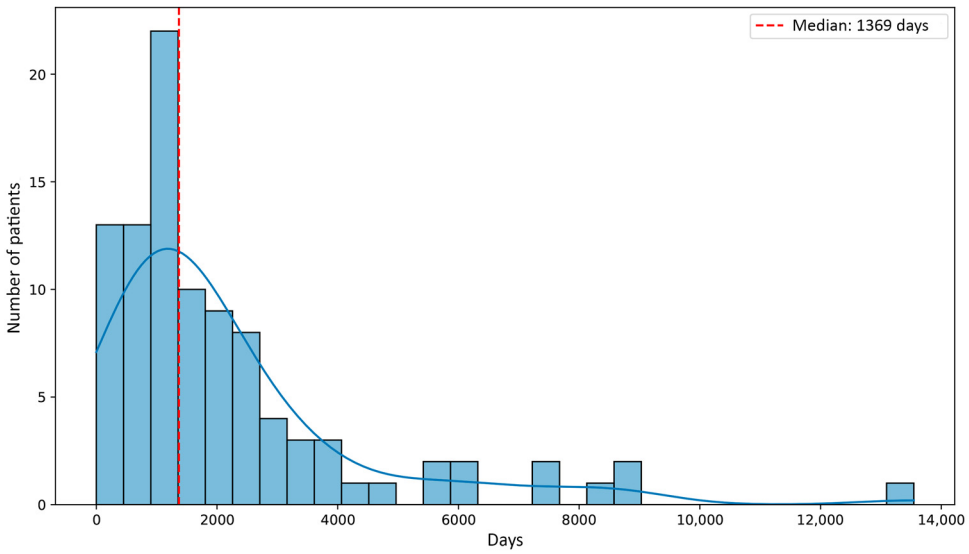


Figure 1. Distribution of time from therapy initiation to first prescription of a bDMARD/JAK inhibitor. The blue solid line represents the kernel density estimate (KDE) curve, showing the smoothed distribution of the time to first bDMARD/JAK inhibitor. The red dashed line indicates the median time to first bDMARD/JAK inhibitor (1369 days). One patient started treatment directly with a bDMARD (certolizumab pegol combined with csDMARDs), reflected as a zero time to first bDMARD.

LEF was used in 88 patients (90.7%), GCs in 78 (80.4%), SSZ in 66 (68.0%), hydroxychloroquine (HCQ) in 65 (67%), while azathioprine (AZA) and GOLD were used in 4 patients each (4.1%). SSZ was the second most common first-line monotherapy agent (12 patients), whereas LEF was most common on the second line (14 patients). The combination "JAK inhibitor + MTX" was observed in 63 patients (64.9%), and all patients received MTX combined with a bDMARD at least once.

A total of 59 switches from MTX to LEF/SSZ after AEs were registered. There were 50 records of IL-6 inhibitor monotherapy and 19 records of JAK inhibitor monotherapy. In

addition, 40 cases of MTX dose reduction after GCs withdrawal were identified (examples: 20→15 mg, 25→15 mg, 20→10 mg).

Patients treated with imported MTX had significantly longer treatment periods (median 16.25 years) compared with Russian-manufactured MTX (median 2.25 years) ($p = 0.0008$). In 23 treatment lines among 6 patients, information about the manufacturer country was missing. When analyzing only the first MTX treatment period, the median duration for imported MTX was 1339 days (IQR 365–2790) versus 442 days (IQR 150–821) for Russian MTX ($p = 0.019$). Analysis of switching patterns showed that patients switched more often from Russian MTX to imported MTX (10 switches) than vice versa (5 switches). Only one case involved switching from imported to Russian MTX with temporary use of both.

3.2. Structure of Treatment Lines and Disease Activity

Subsequently, treatment-line analysis was performed using a processed dataset in which dose changes were not considered new lines ($n = 866$). Overall, 396 lines (45.7%) consisted exclusively of csDMARD/GCs therapy, whereas 470 lines (54.3%) included bDMARDs and/or JAK inhibitors. All patients had at least 4 treatment lines; the maximum number was 19. At the last visit, 95 patients (97.9%) were receiving bDMARDs/JAK inhibitors, while only 2 patients (2.1%) remained on csDMARD/GCs therapy alone.

Among the 470 treatment lines containing bDMARDs or JAK inhibitors, IL-6 inhibitors were most common (127 lines, 27.0%), followed by TNF-α inhibitors (109 lines, 23.2%), JAK inhibitors (89 lines, 18.9%), B-cell inhibitors (rituximab, 82 lines, 17.4%), and T-cell inhibitors (abatacept, 61 lines, 13.0%). GM-CSF and IL-17A inhibitors were observed only once each.

Regarding the structure of the final treatment line, combinations with MTX ($n = 35$) and GCs ($n = 40$) were most common. Disease activity at the last visit according to composite indices is presented in Table 1.

Table 1. Distribution of disease activity according to rheumatoid arthritis activity indices.

Index	Remission	Low Activity	Moderate Activity	High Activity
CDAI	2 (2.1%)	36 (37.1%)	37 (38.1%)	22 (22.7%)
SDAI	4 (4.1%)	34 (35.1%)	40 (41.2%)	19 (19.6%)
DAS28-CRP	34 (35.1%)	10 (10.3%)	43 (44.3%)	10 (10.3%)
DAS28-ESR	19 (19.6%)	14 (14.4%)	42 (43.3%)	22 (22.7%)

Based on median activity index values at the last visit, the lowest disease activity was observed in patients treated with abatacept, levilimab, and olokizumab, whereas the highest values were seen with rituximab and etanercept (Table 2, Figure 2). Moreover, statistically significant between-group differences were not found for most indices (CDAI: $p = 0.2194$; SDAI: $p = 0.1630$; DAS28-CRP: $p = 0.0848$), except for DAS28-ESR ($p = 0.0269$).

Table 2. Rheumatoid arthritis activity at the last visit according to the final-line therapy drug (only bDMARDs/JAK inhibitors).

Drug	Patients	CDAI	SDAI	DAS28-CRP	DAS28-ESR
Abatacept	9	7.0 [6.0; 17.0]	7.0 [6.1; 17.9]	2.5 [2.0; 4.1]	3.3 [3.1; 4.7]
Baricitinib	4	14.0 [10.2; 17.2]	14.6 [10.9; 17.9]	3.7 [3.1; 4.0]	4.2 [3.5; 4.7]
Levilimab	23	9.0 [5.0; 17.0]	9.8 [5.5; 17.0]	2.9 [1.8; 3.5]	3.2 [2.4; 4.0]
Certolizumab pegol	3	14.0 [10.0; 14.0]	16.0 [11.4; 16.1]	4.0 [3.2; 4.0]	4.0 [3.8; 4.5]
Olokizumab	16	9.0 [6.0; 19.0]	9.1 [6.0; 19.0]	2.7 [2.0; 3.6]	2.9 [2.0; 4.2]
Rituximab	28	18.5 [11.0; 24.0]	19.7 [12.0; 27.0]	4.1 [3.2; 4.9]	4.6 [3.8; 5.7]
Etanercept	8	20.5 [12.8; 26.0]	21.4 [12.9; 27.4]	4.2 [3.1; 5.2]	5.2 [3.9; 6.1]
Tofacitinib	4	14.5 [11.5; 20.5]	15.1 [12.5; 20.6]	3.2 [3.1; 3.7]	3.7 [3.1; 4.0]
p (Kruskal–Wallis)		0.2194	0.163	0.0848	0.0269

Note: data are presented as median [Q1; Q3]. Two patients on the last treatment line received HCQ and HCQ + LEF, respectively.

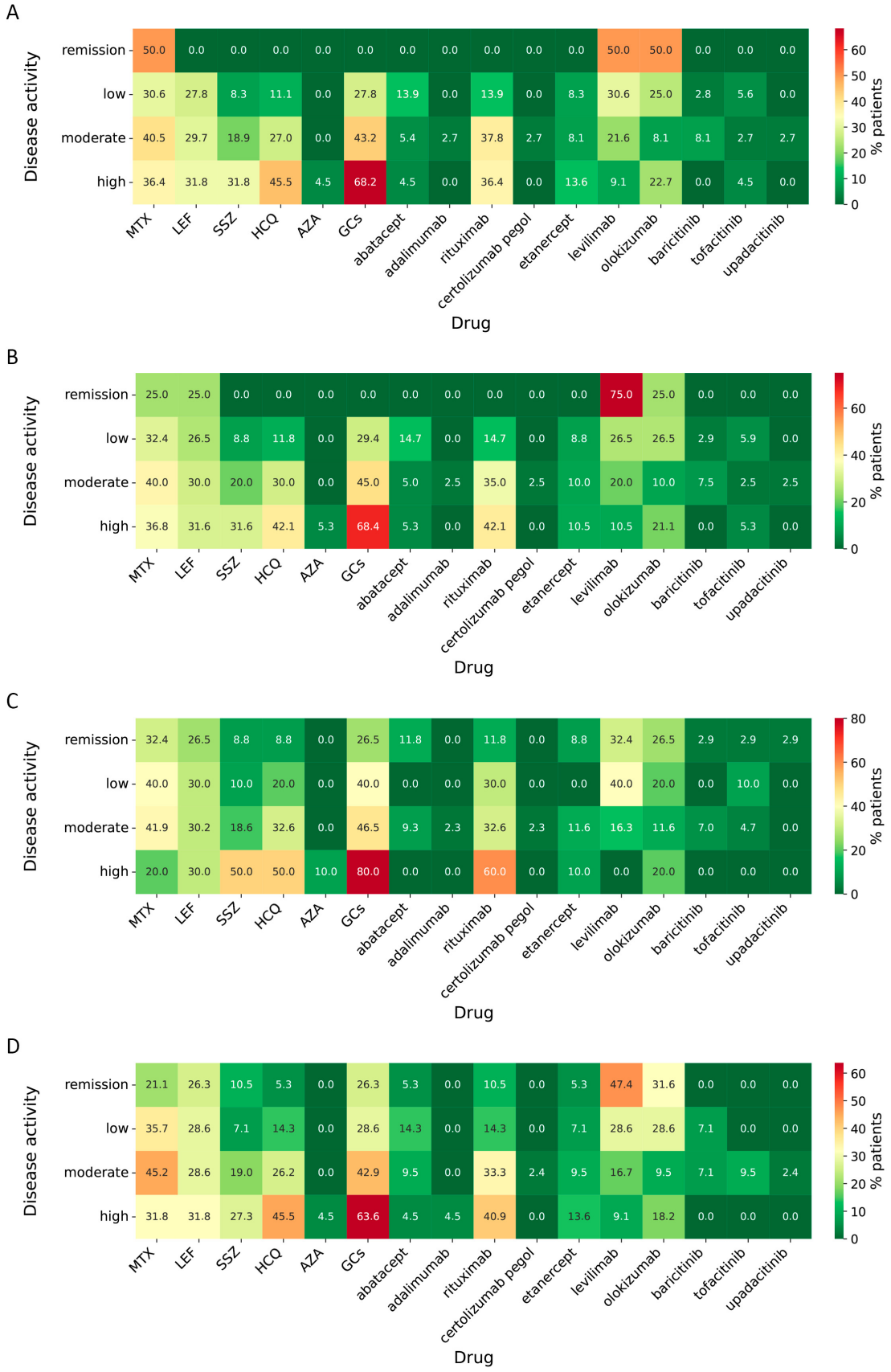


Figure 2. Frequency of drug prescriptions in the last line of therapy depending on disease activity. (**A**) CDAI, (**B**) SDAI, (**C**) DAS28-ESR, (**D**) DAS28-CRP. The *X*-axis shows drugs (csDMARDs/GCs and b/tsDMARDs), and the *Y*-axis shows activity level. Cell color reflects the proportion of patients in the group (0–100%).

3.3. Reasons for Therapy Switching and AEs

Treatment ineffectiveness was the predominant reason for therapy switching, accounting for 506 of 769 transitions (65.8%). A combination of ineffectiveness and AEs was observed in 98 cases (12.7%), isolated AEs in 81 (10.5%), technical inability to continue therapy in 32 (4.2%), discontinuation or interruption for other reasons in 26 (3.4%), achievement of low disease activity in 15 (2.0%), and infectious events in 2 (0.3%). Remission was achieved in one case; however, subsequent loss of response occurred (combination of GCs, SSZ, HCQ, and levilimab), and therefore this case was not counted separately. The reason for switching was unspecified in 9 transitions (1.2%).

csDMARD/GCs therapy was more frequently discontinued due to ineffectiveness compared with biologic/JAK therapy (70.1% vs. 61.3%), whereas technical inability to continue treatment was almost absent among csDMARD/GCs lines (one case in each of two patients vs. 8.0% among biologic/JAK lines). Achievement of treatment target was observed in 3 csDMARD/GCs cases (0.8%) and 12 targeted-therapy cases (3.2%). The frequency of discontinuation due to AEs did not differ between csDMARD/GCs and bDMARD/JAK lines (9.9% and 11.2%, respectively).

The most common AEs were dyspepsia (44 patients, 6.7% of all 1029 records), allergic reactions (3.2%) and elevation of transaminases > 3 × ULN (2.3%). Among allergic reactions, the following specific manifestations were documented: post-injection dyspnoea $n = 5$, urticaria $n = 4$, angioedema $n = 3$, local injection-site reactions $n = 2$, dermatitis/leg rash/pruritus $n = 1$ each. The remaining allergic reactions were recorded as "significant allergic reaction" without further specification. In an unadjusted patient-level comparison, the mean CCI did not differ significantly between patients with and without AEs (2.14 vs. 1.99, $p = 0.929$); however, in the adjusted models described below, comorbidity was associated with AE occurrence and, more strongly, with recurrent AEs.

At least one AE during follow-up was registered in 79 patients (81.4% of the cohort). The mean number of recurrent AEs after the first episode was 1.5, and 65.8% ($n = 52$) experienced repeated AEs: 19 had one recurrent AE, 16 had two, 9 had three, 3 had four, 4 had five, and 1 had seven recurrent episodes.

In the GEE model based on 866 treatment lines grouped by patient and adjusted for age, sex, line number, and CCI, treatment type was not a significant predictor of AE occurrence. The unadjusted OR for AE occurrence on bDMARD/JAK versus csDMARD/GCs lines was 0.657 (95% CI 0.463–0.933); after adjustment, the OR was 0.925 (95% CI 0.630–1.358; $p = 0.690$). Line number was independently associated with AE occurrence (OR 0.895 per line, 95% CI 0.832–0.963; $p = 0.003$), suggesting that the apparent association between treatment type and AEs was largely explained by the earlier position of csDMARD/GCs lines within the treatment sequence. Female sex was associated with higher odds of AEs (OR 3.80, 95% CI 1.66–8.72; $p = 0.002$), and CCI showed a borderline association (OR 1.20 per point, 95% CI 0.99–1.45; $p = 0.062$), while age was not significantly associated with AE occurrence (OR 0.98, 95% CI 0.95–1.01; $p = 0.143$). While treatment type was not associated with AE occurrence, the presence of an AE on the previous treatment line significantly increased the risk of AE occurrence on the current line (adjusted OR 1.72, 95% CI 1.13–2.60; $p = 0.011$). Exposure-adjusted AE incidence rates were 16.7 per 100 patient-years for csDMARD/GCs lines and 15.3 per 100 patient-years for bDMARD/JAK lines, with no statistically significant difference after accounting for exposure time (IRR 1.09 for csDMARD/GCs relative to bDMARD/JAK, 95% CI 0.83–1.45; $p = 0.53$).

After the first AE episode, recurrent AEs occurred in 78.6% of patients receiving csDMARD/GCs therapy (mean number of recurrent AEs 1.79) and in 34.8% of patients receiving b/tsDMARD therapy (mean 0.74). In a per-event model adjusted for line number, age, sex, CCI, and treatment class of the first AE, the treatment class was not a significant

predictor of recurrent AEs (adjusted OR 1.36, 95% CI 0.69–2.68; $p = 0.382$). Line number (OR 0.86 per line, 95% CI 0.77–0.96; $p = 0.008$), age (OR 0.96 per year, 95% CI 0.94–0.99; $p = 0.007$), and CCI (OR 1.33 per point, 95% CI 1.12–1.59; $p = 0.001$) were independently associated with recurrent AEs. These findings suggest that recurrent AEs are driven primarily by patient-level factors and cumulative treatment exposure rather than by the treatment class of the first AE.

For the analysis of therapeutic switches following AEs, temporary treatment lines consisting solely of csDMARDs/GCs between two targeted therapies were considered transitional and were not treated as independent switching pathways. In such cases, the final transition between targeted treatment mechanisms was analyzed. Following the occurrence of AEs during TNF inhibitor therapy, 47.8% of cases involved switching within the same class, while 52.2% involved switching to another class of targeted therapy; however, 29.2% of patients temporarily received no b/tsDMARD therapy. After AEs during IL-6 inhibitor therapy, 44% of cases involved switching to another molecule within the same class, whereas 56% involved switching to another class of biologic/JAK inhibitor therapy; nevertheless, 40% of patients spent a period on csDMARD/GCs-only therapy following the AE.

3.4. Treatment Line Survival, Transitions Between Drug Classes, Drug Discontinuation Rates, and Cluster Analysis

The median observed duration of treatment lines containing only csDMARDs/GCs was 334 days (IQR 122–730), compared with 271 days (IQR 148–686) for biologic/JAK-containing lines (without censoring at the patient's last observation day). After accounting for censored observations, the median duration was 335 days in both groups; the log-rank test showed no statistically significant difference ($p = 0.4313$) (Figure 3); however, because treatment lines within a patient are not independent, this p-value is reported for descriptive comparison only. Formal inference was based on a cluster-robust Cox model (see below).

MTX-containing treatment lines, excluding the final ongoing treatment phase, demonstrated a median survival of 365 days (IQR 126–730) compared with 319 days (IQR 136–671) for non-MTX lines, with no significant difference detected by the log-rank test ($p = 0.8819$); this p-value is descriptive, as for the previous comparison.

In a cluster-robust Cox proportional hazards model adjusted for treatment type, line number, age, sex, and CCI, no covariate was significantly associated with treatment-line survival (treatment type HR 0.88, 95% CI 0.74–1.04, $p = 0.13$; all other covariates $p > 0.05$). Concordance was 0.53. Results were consistent with the naive Cox model without clustering, confirming the robustness of the Kaplan–Meier estimates.

Analysis by treatment line number showed that csDMARD/GCs therapy demonstrated a median duration of 365 days on the first line, 320 days on the second line, 304–365 days on lines 3–5, 304–366 days on lines 6–7, followed by a decline to 182–213 days on later lines (8–11). For b/tsDMARDs therapy, the median duration was 245 days on the second line, 304 days on the third line, reached 365 days on the fourth line and 290 days on the fifth line, then varied between 260 and 366 days on lines 6–9, decreasing to 234–240 days on lines 10–11 and to 127 days by the thirteenth line. Interpretation of late-line therapy ($\geq$8) is limited by the small number of observations, although the highest median duration was observed on the twelfth line (406 days).

Analysis of class distribution across treatment lines showed that TNF-α inhibitors were predominantly prescribed in early lines (2–5), whereas IL-6 inhibitors dominated in later lines (7–10) (Figure 4A). Rituximab prescriptions peaked on the sixth line (16 prescriptions), while JAK inhibitors were actively used on lines 5–8.

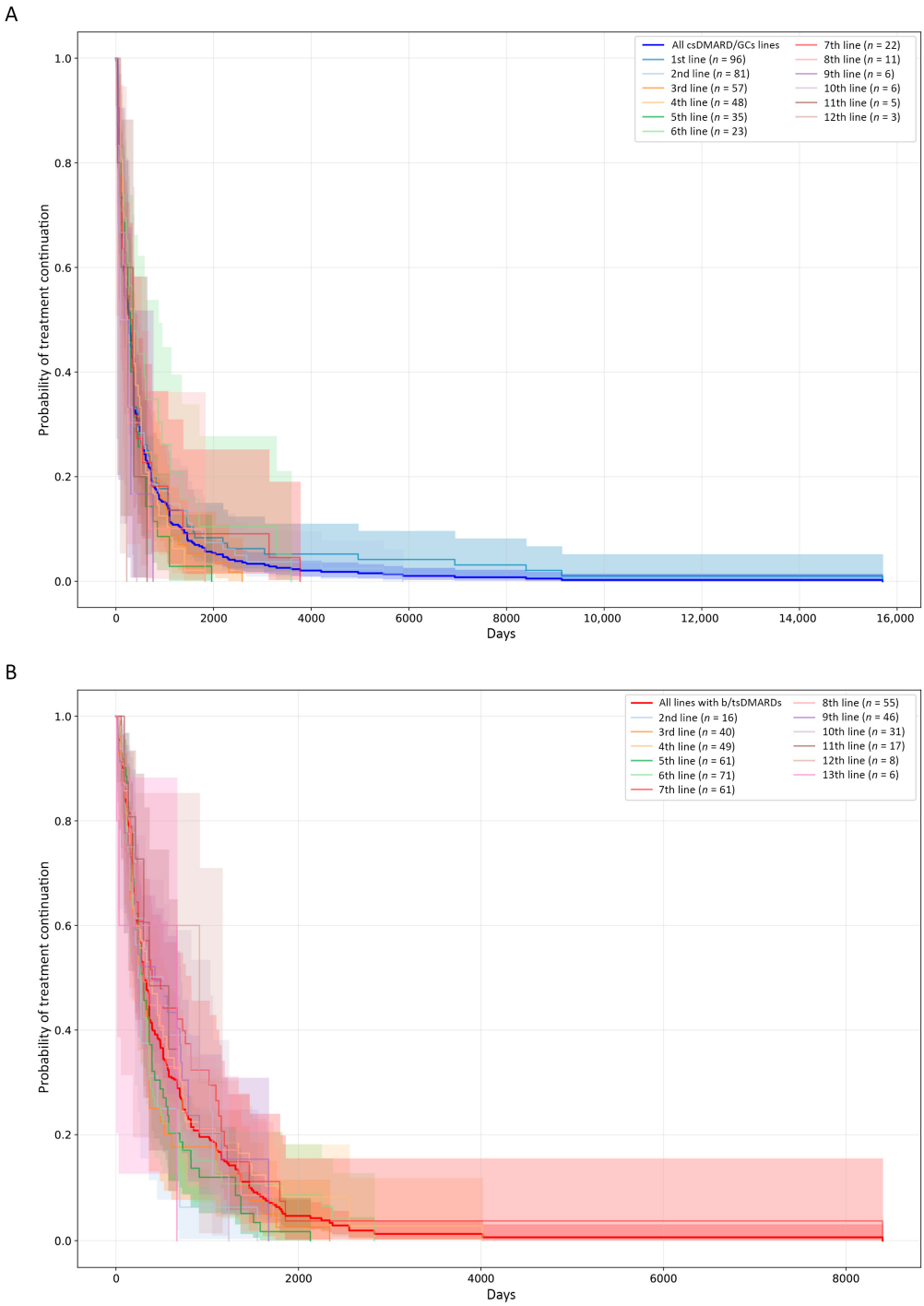


Figure 3. Kaplan–Meier curves reflecting retention duration of each treatment line (censoring defined as the start of the next treatment line or the last documented visit, whichever came first). In this analysis, a treatment line is defined as any change in therapy (addition, discontinuation, or replacement of any medication; dose adjustments alone were not considered new lines). (**A**) Survival of treatment lines containing only csDMARDs/GCs according to line number. (**B**) Survival of treatment lines containing biologics or JAK inhibitors according to line number. Note: The 1st line is not displayed in panel B because only one patient started therapy directly with a bDMARD (n = 1), which was insufficient to construct a Kaplan–Meier curve.

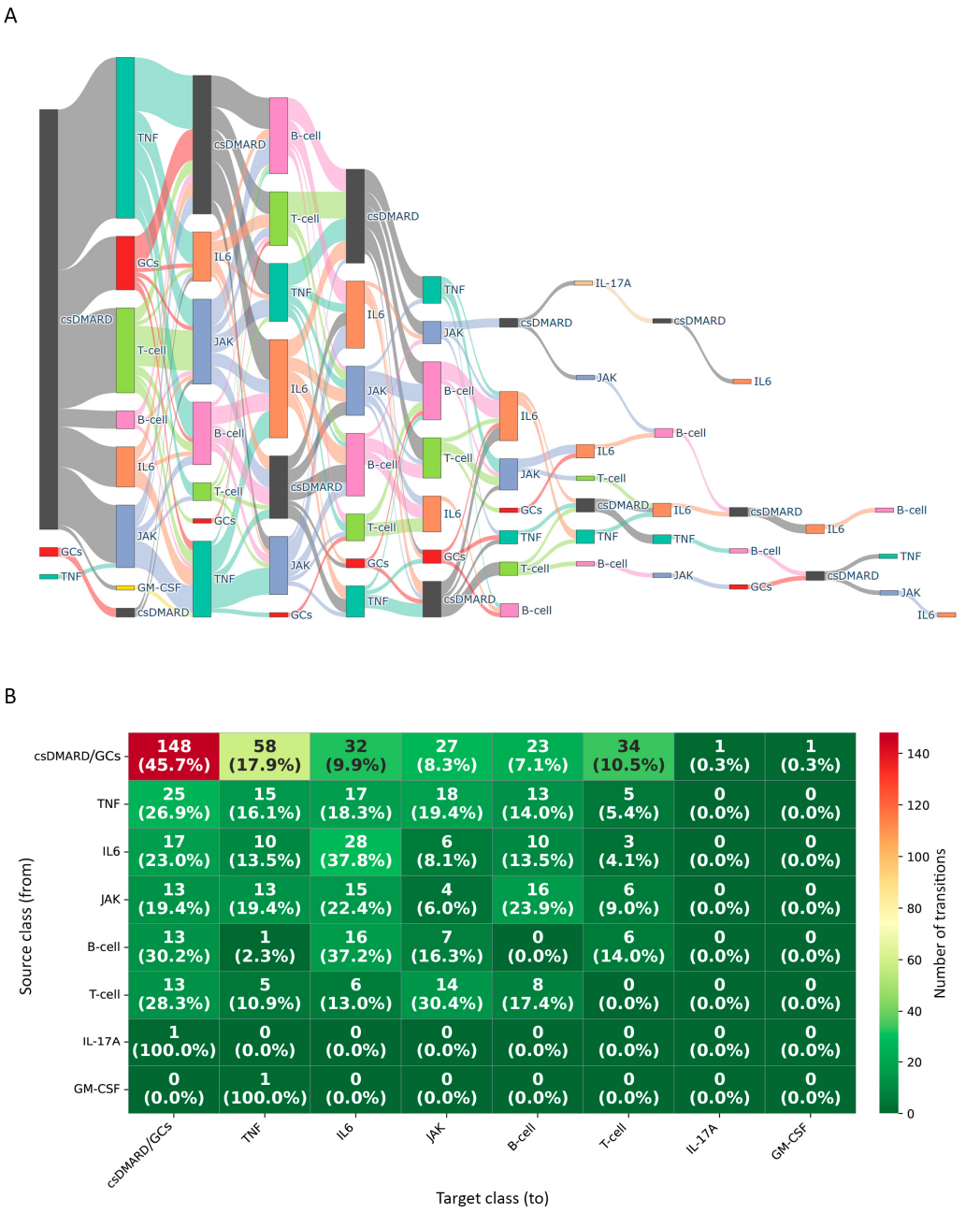


Figure 4. Graphical representation of treatment-line transitions. (**A**) Sankey diagram: flow width is proportional to the number of transitions. For clarity, consecutive lines within the same drug class were merged; therefore, the number of lines shown here is smaller than the 866 treatment lines used in the primary analysis. (**B**) Heatmap: cell color reflects the absolute number of transitions (scale shown on the right). Within-class transitions were included. The category "csDMARD/GCs" includes both csDMARD/GCs monotherapy and csDMARD/GCs combination therapy.

Analysis of transitions between drug classes demonstrated that the most frequent switches were from csDMARD/GCs therapy to TNF-α inhibitors (58 transitions), T-cell inhibitors (34), IL-6 inhibitors (32), and JAK inhibitors (27) (Figure 4B). A transition was defined only as drug discontinuation; addition or withdrawal of concomitant drugs was not considered. Return to csDMARD/GCs therapy most frequently occurred after TNF-α inhibitors (25 transitions) and IL-6 inhibitors (17), whereas within-class switching was most common for csDMARDs/GCs (148 of 394 transitions, 37.6%), IL-6 inhibitors (28 of 87, 32.2%), and TNF-α inhibitors (15 of 98, 15.3%). Such transitions were uncommon for JAK inhibitors (4 of 80, 5%).

Analysis of treatment transitions depending on the presence of AEs on the previous treatment line showed that when AEs occurred during TNF-α inhibitor therapy, switching remained within the TNF-α inhibitor class in 37.5% of cases, to another targeted therapy in 33.3%, and back to csDMARD/GCs therapy alone in 29.2%. In cases of AEs during IL-6 inhibitor therapy, switching back to csDMARD/GCs therapy occurred in 40% of cases, to another targeted therapy in 28%, and within the same class in 32%. If AEs occurred during a csDMARD/GCs line, switching most frequently occurred to TNF-α inhibitors (10.4%).

Analysis of TNF-α inhibitor prescriptions showed that in 59 of 109 treatment lines (54.1%), these drugs were prescribed without MTX, despite evidence that concomitant MTX reduces immunogenicity and improves drug survival [11]. However, many of these lines still included alternative csDMARDs: the most frequent MTX-free combinations were LEF + etanercept (6 lines) and LEF + adalimumab (6 lines). True monotherapy or GCs-only combinations included GCs + etanercept (5 lines), and etanercept monotherapy (5 lines). After MTX-related AEs were documented, physicians continued MTX in combination with a TNF-α inhibitor in 57.1% of cases, whereas MTX was discontinued in 42.9%. For IL-6 inhibitors, only 30 monotherapy lines were identified, and 80 of 127 lines (63.0%) did not include combination therapy with MTX.

At the level of individual drugs, MTX and GCs remained the most stable therapeutic background treatments: MTX was continued into subsequent lines in 293 of 392 transitions (74.7%), and GCs in 334 of 384 transitions (87%). Among targeted therapies, the highest discontinuation rates were observed for adalimumab, infliximab, golimumab, and certolizumab pegol (100% discontinuation, never continued into the next line), followed by tocilizumab (97.2%), sarilumab (90.9%), etanercept (90.0%), baricitinib (89.3%), abatacept (86.8%), tofacitinib (80.0%), and rituximab (80.0%). Frequencies of discontinuation and the main reasons for therapy cessation are presented in Table 3. The rate of re-initiation after prior discontinuation varied widely (0–41%). Two conventional synthetic DMARDs (azathioprine and GOLD) and eight targeted therapies (baricitinib, infliximab, certolizumab pegol, golimumab, upadacitinib, otilimab, sirukumab, and netakimab) were never resumed after withdrawal, indicating definitive replacement. In contrast, the highest re-initiation rates were observed for MTX (41%), SSZ (26.3%), and sarilumab (25%), suggesting that these agents are occasionally reconsidered after a treatment break.

To identify treatment patterns, patients were clustered using four approaches appropriate for binary data: K-modes, MCA followed by K-means, hierarchical clustering with Gower distance (average linkage), and hierarchical clustering with Dice distance (average linkage).

Hierarchical clustering with Dice distance collapsed all 97 patients into a single cluster across all tested thresholds (0.3–0.7). Gower-based clustering produced 8 clusters at a threshold of 0.2, but these collapsed to 3 clusters at 0.3 and to a single cluster at $\geq$0.4, indicating that the treatment profiles in this cohort are largely homogeneous.

K-modes clustering identified 3 stable treatment patterns at $k = 3$ (silhouette score 0.377; bootstrap stability 0.398, with one cluster exceeding 0.75). Increasing k to 5 produced a marginally higher silhouette (0.427) but substantially lower stability (0.244), indicating overfitting; $k = 3$ was therefore retained. MCA followed by K-means also yielded a 3-cluster solution with the highest overall bootstrap stability (0.501), although clusters were not well separated in Jaccard space (silhouette 0.000).

Table 3. Frequency of discontinuation of individual drugs and the main reasons for therapy cessation.

Drug	Transitions with Drug (*n*)	Discontinued (*n*)	Continued (*n*)	Discontinuation Rate (%)	Return After Discontinuation (%)	Main Reason for Discontinuation
Glucocorticoids	384	50	334	13	25	Ineffectiveness (60%)
Conventional synthetic DMARDs						
Methotrexate	392	99	293	25.3	41	Ineffectiveness (38.4%)
Leflunomide	208	73	135	35.1	19.4	Ineffectiveness (47.9%)
Hydroxychloroquine	166	50	116	30.1	19.1	Ineffectiveness (56%)
Sulfasalazine	156	66	90	42.3	26.3	Ineffectiveness (59.1%)
Gold salts	4	4	0	100	0	Ineffectiveness (50%)/AEs (50%)
Azathioprine	3	3	0	100	0	Ineffectiveness (33.3%)/AEs (33.33%)/Technical impossibility (33.33%)
Biologics and JAK inhibitors						
Rituximab	55	44	11	80	20.5	Ineffectiveness (79.5%)
Abatacept	53	46	7	86.8	9.3	Ineffectiveness (65.2%)
Etanercept	50	45	5	90	6.8	Ineffectiveness (68.9%)
Tofacitinib	50	40	10	80	14.3	Ineffectiveness (60%)
Tocilizumab	36	35	1	97.2	9.7	Technical impossibility (45.7%)
Adalimumab	28	28	0	100	8	Ineffectiveness (75%)
Baricitinib	28	25	3	89.3	0	Ineffectiveness (84%)
Olokizumab	23	16	7	69.6	6.3	Ineffectiveness (56.3%)
Levilimab	16	12	4	75	8.3	Ineffectiveness (75%)
Infliximab	12	12	0	100	0	Ineffectiveness (75%)
Sarilumab	11	10	1	90.9	25	Technical impossibility (60%)
Certolizumab pegol	5	5	0	100	0	Ineffectiveness (50%)/AEs (50%)
Golimumab	3	3	0	100	0	Ineffectiveness (100%)
Upadacitinib	2	2	0	100	0	Ineffectiveness (100%)
Otilimab	1	1	0	100	0	Discontinuation/pause (100%)
Sirukumab	1	1	0	100	0	Ineffectiveness (100%)
Netakimab	1	1	0	100	0	Ineffectiveness (100%)

Note: Reasons for discontinuation were extracted from the final record of each treatment line. Discontinuation rate = number of discontinued lines/number of lines containing the drug. Return after discontinuation = number of patients who resumed the drug after at least one documented discontinuation/number of patients with at least one discontinuation.

The three K-modes clusters differed primarily in the presence of JAK inhibitors and HCQ on a common background of MTX, bDMARDs, and GCs (Figure 5):

- Cluster 1 (n = 42, 43.3%)—JAK-containing, HCQ-containing pattern: all patients received MTX, bDMARDs, JAK inhibitors, and HCQ; 98% received LEF, 74% SSZ, 76% GCs.
- Cluster 2 (n = 32, 33.0%)—JAK-containing, HCQ-free pattern: all patients received MTX and bDMARDs; 84% LEF, 62% SSZ, 66% JAK inhibitors, 84% GCs; no patient received HCQ.
- Cluster 3 (n = 23, 23.7%)—HCQ-containing, JAK-free pattern: all patients received MTX, bDMARDs, and HCQ; 87% LEF, 65% SSZ, 83% GCs; no patient received JAK inhibitors.

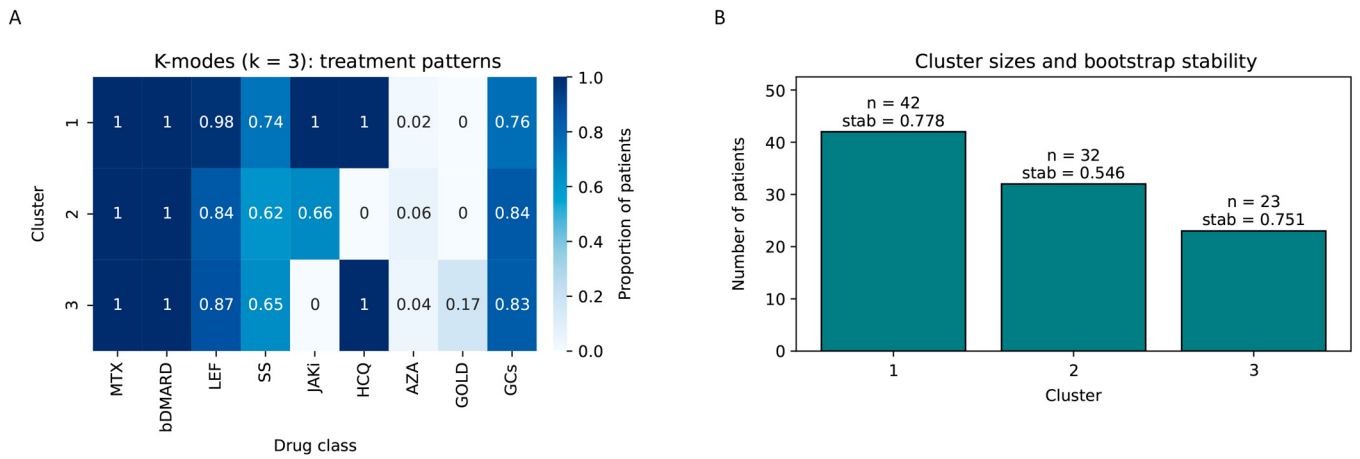


Figure 5. Exploratory treatment patterns in patients with difficult-to-treat rheumatoid arthritis identified by K-modes clustering (k = 3). (**A**) Heatmap of prescription frequencies of nine drug classes across the three clusters. Cell color reflects the proportion of patients within each cluster receiving the corresponding drug (0–1). (**B**) Cluster sizes with bootstrap co-clustering stability (300 resamples). Clusters 1 exceeded the stability threshold of 0.75; Clusters 2 and 3 were moderately stable. Abbreviations: JAKi—JAK inhibitors.

Only Cluster 1 demonstrated bootstrap stability > 0.75 (0.778). Clusters 2 and 3 were moderately stable (0.546 and 0.751, respectively, before excluding self-pairs; see Table S1). Cluster 1 was the most compact (mean intracluster Jaccard distance 0.123; see Table S1), cluster 2 was the least compact (0.273), and cluster 3 was intermediate (0.218).

These results indicate that treatment patterns in this D2T-RA cohort are largely homogeneous, with the principal axis of variation defined by the use of JAK inhibitors versus HCQ. We therefore report three exploratory treatment patterns rather than distinct phenotypes. External validation in independent D2T-RA cohorts is required before these patterns can be considered clinically meaningful subgroups.

4. Discussion

The main strengths of this study include its real-world setting, the use of a large city registry (54,967 patients), the detailed longitudinal capture of treatment lines (866 lines, up to 19 per patient), the integration of clinical, laboratory, and patient-reported data, and the application of GEE and cluster-robust models that account for within-patient correlation. The analysis of treatment trajectories over a prolonged follow-up period provides insights that complement those from randomized trials.

The obtained data indicate that the D2T-RA cohort was characterized by frequent treatment switching (including within the same therapeutic class) and variability in clinical response. All patients eventually received targeted therapy (bDMARDs or JAK inhibitors); however, the median time from the first drug to initiation of targeted therapy was 3.7 years, suggesting delayed treatment escalation in part of the cohort compared with EULAR recommendations [4]. The recommendations [4] also emphasize that JAK inhibitors require careful risk assessment (cardiovascular events, malignancies, thromboembolic complications), especially in patients older than 65 years and those with additional risk factors. In our cohort, tofacitinib, baricitinib, and upadacitinib were predominantly used in later treatment lines (mainly lines 5–8), reflecting a cautious therapeutic approach.

The predominance of inefficacy as the primary reason for treatment switching (65.8% of all switches and an additional 12.7% combined with AEs) is consistent with published literature showing that insufficient clinical response remains the main limitation in RA treatment [7]. At the same time, the rate of treatment discontinuation due to isolated AEs

(10.5%) was comparable to previously published data [8]. However, these findings should be interpreted with caution. According to Roodenrijs et al., a substantial proportion of patients with D2T-RA have concomitant fibromyalgia (38%), which may mimic persistent RA activity and be erroneously interpreted as treatment failure [12]. Similarly, Qi et al. demonstrated that non-inflammatory pain is significantly more common among patients with D2T-RA than among those without D2T-RA (28% vs. 8%) [13]. Together, these observations highlight the importance of careful differential diagnosis between persistent synovitis and central sensitization in patients with multiple therapeutic failures.

The absence of statistically significant differences in treatment-line survival between csDMARD/GCs and bDMARD/JAK inhibitor therapies, despite numerically shorter raw durations of targeted-therapy lines, likely reflects selection bias (including the effect of censoring). More severe and refractory patients were more likely to receive targeted therapy at later stages, thereby reducing the observed duration of its use. Nevertheless, prior to the final treatment stage (when patients entered the study), the median duration of treatment lines containing only csDMARDs/GCs exceeded that of bDMARD/tsDMARD lines by 63 days before censoring.

D'Onofrio et al. reported that among patients with early RA who escalated to b/tsDMARD therapy after methotrexate failure (median time to b/tsDMARD initiation: 19 months), the prevalence of D2T-RA reached 29% after a median follow-up of 72.6 months [14]. These findings suggest that, although delayed treatment escalation may contribute to prolonged disease burden, timely escalation alone is unlikely to completely prevent the development of D2T-RA. In addition, Ueno et al. demonstrated that early initiation of IL-6 inhibitors in high-risk patients was associated with a 52% reduction in the risk of progression to D2T-RA [15]. Consistent with these observations, a high proportion of patients receiving levilimab or olokizumab achieved remission or low disease activity at the final treatment line in our cohort. Furthermore, our findings are in agreement with those reported by Takanashi et al., who showed that the use of IL-6 inhibitors was associated with resolution of the D2T-RA state [16]. Published data suggest a potential role for IL-6 blockade in preventing progression to D2T-RA [15], whereas our findings and those of Takanashi et al. [16] support its role in improving outcomes in established D2T-RA. However, these hypotheses require prospective validation.

In our cohort, the lowest disease activity at the final treatment line was observed among patients receiving IL-6 inhibitors (olokizumab and levilimab) and abatacept, whereas the highest disease activity was recorded in the rituximab and etanercept groups. This observation appears to contrast with the findings of Hecquet et al. [17], who found that rituximab and JAK inhibitors achieved the most favorable outcomes in patients with EULAR-defined D2T-RA, with remission rates of approximately 27%, while IL-6 inhibitors were associated with remission in only 12% of patients. However, this apparent discrepancy is likely attributable to differences in treatment strategies and patient selection. In our cohort, rituximab was predominantly prescribed in later treatment lines, with a peak at the sixth line, and was therefore more commonly used in patients with multiple previous treatment failures and more refractory disease. In addition, the timely administration of rituximab infusions may have influenced outcomes in this cohort, as delays in infusion scheduling could compromise its real-world effectiveness. In contrast, although IL-6 inhibitors were also mainly used in advanced treatment lines, they were associated with lower disease activity at the final assessment. Consequently, the observed differences in outcomes may reflect confounding by indication and variations in prescribing patterns across centers rather than true differences in drug efficacy. However, because treatment allocation to final-line therapies was not randomized and several drug groups included only a small number of patients, differences in disease activity between treatments should

be interpreted with caution. These findings should therefore be considered exploratory and hypothesis-generating rather than evidence of comparative effectiveness.

Several limitations of the present study should be considered. First, the retrospective design is inherently associated with missing data and documentation errors (1.2% of treatment switches lacked a documented reason). AEs were not graded using a standardized severity scale (e.g., CTCAE), and clinically significant laboratory abnormalities were not analyzed as a separate category, reflecting the lack of systematic severity documentation in the source records. Second, there remains a risk of influence from unobserved factors, including pharmacogenetic determinants. Third, treatment duration was not included as a covariate in the AE models because it is a mediator rather than a confounder: it lies on the causal pathway between treatment type and AE occurrence, and adjusting for it could introduce collider bias. Exposure-adjusted incidence rates were therefore calculated as a sensitivity analysis and showed no significant difference between treatment categories. Fourth, GCs dose and duration were not modeled separately, as GCs form part of the comparator category (csDMARD/GCs); this may have influenced the observed associations with AEs. Fifth, the study included only residents of the Russian Federation (all Caucasian ethnicity), which may limit generalizability to other populations. Finally, the use of IL-17 inhibitors and AZA was driven by evolving diagnostic concepts and specific clinical scenarios, reflecting real-world complexity in managing refractory RA, which limits direct comparisons with standard treatment algorithms.

5. Conclusions

Patients with D2T-RA demonstrate a pronounced sequence of treatment modifications, with inefficacy remaining the predominant reason for therapy switching. csDMARDs represent the initial component of treatment; however, the majority of patients subsequently transition to bDMARDs and JAK inhibitors. In line with EULAR recommendations, regular assessment of csDMARD efficacy every 3 months is essential to guide timely therapeutic escalation, particularly in the context of D2T-RA. Long-term combination therapy should be considered appropriate only when disease activity control is achieved and GCs therapy is no longer required.

AEs are frequent in patients with D2T-RA, and their occurrence during a previous treatment line is associated with an increased risk of recurrence. After adjustment for line number, age, sex, and comorbidity burden, treatment modality was not a significant predictor of AE occurrence. The development of specific management protocols for RA patients with a high comorbidity burden appears warranted.

A high proportion of TNF-α inhibitor prescriptions without concomitant methotrexate should be noted, which is inconsistent with the current treatment paradigm for RA. Overall, our data indicate a tendency toward insufficient combination of previously ineffective csDMARDs, such as methotrexate, with JAK inhibitors or bDMARDs, highlighting the need for optimization of treatment strategies. Within-class switching among IL-6 inhibitors was frequent in our cohort. It cannot be excluded that the observed clinical effects were partly attributable to within-class switching and to the specific component of the IL-6 pathway targeted (receptor blockade vs. direct IL-6 inhibition). These findings require validation in larger cohorts.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biologics6040030/s1, Table S1: Compactness and bootstrap stability of the three K-modes treatment patterns (k = 3).

Author Contributions: Conceptualization, A.I.Z. and V.I.M.; data curation, A.I.Z., E.N.S., Y.A.G. and V.V.D.; formal analysis, A.I.Z. and A.A.B.; software, V.V.D. and A.A.B.; investigation, E.N.S., Y.A.G.

and V.V.D.; writing—original draft preparation, A.I.Z. and A.A.B.; writing—review and editing, V.I.M.; supervision, V.I.M. All authors contributed equally to all stages of the work and manuscript preparation. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
AEs	Adverse events
ANA	Antinuclear antibodies
AZA	Azathioprine
bDMARDs	Biologic disease-modifying antirheumatic drugs
CCI	Charlson comorbidity index
CDAI	Clinical disease activity index
CI	Confidence interval
CRP	C-reactive protein
csDMARDs	Conventional synthetic disease-modifying antirheumatic drugs
D2T-RA	Difficult-to-treat rheumatoid arthritis
DAS28	Disease activity score in 28 joints
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
GCs	Glucocorticoids
GEE	Generalized estimating equations
GOLD	Gold salts
HCQ	Hydroxychloroquine
HR	Hazard ratio
IL-6	Interleukin-6
IQR	Interquartile range
IRR	Incidence rate ratio
JAK	Janus kinase
LEF	Leflunomide
MCA	Multiple correspondence analysis
MTX	Methotrexate
OR	Odds ratio
RDCI	Rheumatic disease comorbidity index
RF	Rheumatoid factor
SDAI	Simplified disease activity index
SSZ	Sulfasalazine
TNF-α	Tumor necrosis factor-α
tsDMARDs	Targeted synthetic disease-modifying antirheumatic drugs

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