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DRUG SURVIVAL OF BIOLOGIC AND TARGETED SYNTHETIC DMARDS IN PATIENTS WITH RHEUMATOID ARTHRITIS: REAL-WORLD EVIDENCE STUDY.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by progressive joint destruction, functional disability, and reduced quality of life. Over the past two decades, the introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) has significantly improved clinical outcomes in patients with moderate to severe RA. However, despite their proven efficacy in randomized controlled trials (RCTs), long-term treatment success in routine clinical practice remains heterogeneous.

RCTs are conducted under highly controlled conditions with strict inclusion and exclusion criteria, which may limit their generalizability to real-world clinical settings. In daily practice, treatment continuation is influenced not only by clinical efficacy but also by safety profile, patient adherence, comorbidities, and physician decision-making. Therefore, real-world evidence has become increasingly important to evaluate the long-term performance of antirheumatic therapies.

Drug survival, also referred to as drug retention, is defined as the duration of time a patient continues treatment with a given drug before discontinuation for any reason. This composite endpoint reflects overall treatment effectiveness by integrating efficacy, tolerability, safety, and patient satisfaction. As such, drug survival has been widely used as a surrogate marker of real-world effectiveness in chronic diseases, particularly in RA.

Several observational studies and national registry analyses have demonstrated significant differences in drug survival among various classes of bDMARDs and tsDMARDs. Tumor necrosis factor inhibitors (TNFi), interleukin-6 inhibitors, and Janus kinase inhibitors show variable retention rates depending on treatment line, patient characteristics, and healthcare system factors. Findings published in leading rheumatology journals such as Annals of the Rheumatic Diseases, Rheumatology, and The Lancet Rheumatology highlight the growing relevance of drug survival analysis in treatment optimization.

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In addition to its clinical value, drug survival plays an important role in pharmacoeconomic evaluations. Higher drug retention is often associated with lower switching rates, reduced healthcare resource utilization, and improved cost-effectiveness. Consequently, drug survival outcomes are increasingly incorporated into cost-effectiveness and budget impact models.

The objective of the present study is to evaluate the drug survival of biologic and targeted synthetic DMARDs in patients with rheumatoid arthritis in real-world clinical practice and to identify factors associated with treatment discontinuation.

Materials and Methods

Study Design

This study was conducted as a retrospective observational real-world analysis. Data were collected from routine clinical practice, reflecting treatment patterns outside randomized controlled trial settings. The study period covered patients who initiated biologic or targeted synthetic disease-modifying antirheumatic drugs (bDMARDs or tsDMARDs) between January 2018 and December 2024.

Study Population Adult patients (≥18 years) diagnosed with rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria were included in the analysis. Patients were required to have received at least one dose of a bDMARD or tsDMARD and to have a minimum follow-up period of three months.

Exclusion criteria included:

- incomplete clinical data,
- participation in interventional clinical trials,
- discontinuation due to non-medical reasons unrelated to treatment effectiveness or safety (e.g., administrative issues).

Treatment Exposure

Patients were treated with one of the following drug classes:

- tumor necrosis factor inhibitors (TNFi),
- interleukin-6 inhibitors,
- Janus kinase (JAK) inhibitors.

Both first-line and subsequent lines of biologic or targeted therapy were included. Concomitant use of conventional synthetic DMARDs and glucocorticoids was permitted.

Outcome Measures The primary outcome was drug survival, defined as the time (in months) from treatment initiation to permanent discontinuation of the drug for any reason. Discontinuation reasons were categorized as:

- lack or loss of effectiveness,
- adverse events,
- achievement of sustained remission,

• other clinical reasons.

Patients who continued therapy at the end of the observation period were censored.

Statistical Analysis

Descriptive statistics were used to summarize baseline demographic and clinical characteristics. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, while categorical variables were presented as frequencies and percentages.

Drug survival was analyzed using the Kaplan–Meier method, and survival curves were compared between treatment groups using the log-rank test. Multivariable Cox proportional hazards regression analysis was performed to identify predictors of treatment discontinuation, including age, sex, disease duration, baseline disease activity, treatment line, and drug class. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

A p-value <0.05 was considered statistically significant. All statistical analyses were performed using standard statistical software.

Ethical Considerations The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective and anonymized nature of the data, informed consent was waived in accordance with local ethical regulations. Approval was obtained from the institutional ethics committee.

Results

A total of 20 patients with rheumatoid arthritis were included in the study. The mean age of the patients was 52.4 ± 9.1 years, and the majority were female (75%). The median disease duration at the time of initiation of biologic or targeted synthetic therapy was 6.5 years. Baseline disease activity was high, with a mean DAS28 score of 5.6 ± 0.8.

Patients were equally divided into two treatment groups, with 10 patients receiving tumor necrosis factor inhibitors and 10 patients receiving non-TNF therapies, including interleukin-6 inhibitors or Janus kinase inhibitors. Biologic or targeted therapy was prescribed as first-line treatment in 60% of patients, while the remaining patients received these agents as second or subsequent lines of therapy.

During the follow-up period, treatment discontinuation occurred in 7 patients (35%). The overall drug survival rate was 75% at 12 months and decreased to 65% at 24 months. The median drug survival time for the overall cohort was not reached within the observation period, indicating sustained treatment continuation in more than half of the patients.

Comparative analysis demonstrated a higher drug survival rate in the non-TNF therapy group compared with the TNF inhibitor group. At 24 months, 80% of

patients receiving non-TNF therapies remained on treatment, whereas drug survival in the TNF inhibitor group was 50%. Although this difference suggested a trend toward improved retention with non-TNF therapies, it did not reach statistical significance, likely due to the limited sample size.

The most common reason for treatment discontinuation was lack or loss of effectiveness, accounting for 57% of discontinuations. Adverse events were responsible for 29% of treatment cessations, while sustained clinical remission accounted for the remaining 14%.

In exploratory Cox proportional hazards regression analysis, treatment with TNF inhibitors was associated with a higher risk of drug discontinuation compared with non-TNF therapies. Higher baseline disease activity was also associated with an increased likelihood of treatment discontinuation. However, these associations did not achieve statistical significance, reflecting the limited statistical power of the study.

Discussion

In this real-world observational study, drug survival of biologic and targeted synthetic DMARDs was evaluated in a small cohort of patients with rheumatoid arthritis. The main finding of the study was that non-TNF therapies, including interleukin-6 inhibitors and Janus kinase inhibitors, demonstrated higher drug survival compared with tumor necrosis factor inhibitors over a 24-month follow-up period. Although the difference did not reach statistical significance, a clear trend toward improved treatment retention was observed in the non-TNF group.

Drug survival is considered a composite indicator reflecting overall treatment effectiveness, integrating clinical efficacy, safety, tolerability, and patient adherence. Unlike randomized controlled trials, real-world studies capture routine clinical decision-making and therefore provide valuable insights into long-term treatment performance. Our findings are consistent with previously published real-world data reported in leading rheumatology journals such as Annals of the Rheumatic Diseases and Rheumatology, where differences in drug retention among biologic classes have been repeatedly demonstrated.

The higher drug survival observed in the non-TNF therapy group may be explained by several factors. Interleukin-6 inhibitors and JAK inhibitors have shown rapid and sustained suppression of disease activity, including improvement in systemic inflammatory markers, which may contribute to better perceived effectiveness by both patients and physicians. In addition, these agents are often prescribed after TNF inhibitor failure, suggesting a more targeted approach in selected patient populations, which may further enhance treatment retention.

In the present study, lack or loss of effectiveness was the most frequent reason for treatment discontinuation, followed by adverse events. This pattern aligns with previous registry-based analyses, in which inefficacy has been identified as the primary driver of biologic treatment switching in RA. Discontinuation due to sustained remission was observed in a minority of patients, reflecting the chronic and relapsing nature of the disease in routine clinical practice.

Exploratory regression analysis suggested an increased risk of discontinuation among patients treated with TNF inhibitors and those with higher baseline disease activity. Although these associations did not achieve statistical significance, likely due to the limited sample size, they are biologically plausible and supported by larger observational studies. Patients with higher inflammatory burden at baseline may require more potent or mechanism-specific therapies to achieve durable disease control.

Beyond its clinical implications, drug survival has important pharmacoeconomic relevance. Higher treatment retention is commonly associated with reduced switching rates, fewer healthcare resource utilizations, and improved cost-effectiveness. Therefore, incorporating drug survival outcomes into pharmacoeconomic models may improve the accuracy of real-world cost-effectiveness assessments.

Several limitations of this study should be acknowledged. The small sample size limited the statistical power and precluded definitive conclusions regarding comparative effectiveness. The retrospective design and potential confounding factors inherent to real-world data must also be considered. Nevertheless, the study provides valuable preliminary evidence and may serve as a basis for larger prospective investigations.

In conclusion, this real-world analysis suggests that non-TNF biologic and targeted synthetic therapies may offer improved drug survival compared with TNF inhibitors in patients with rheumatoid arthritis. Drug survival remains a meaningful and practical endpoint for evaluating long-term treatment performance in routine clinical practice and may support both clinical decision-making and pharmacoeconomic evaluations.

Conclusion

In this real-world study of 20 patients with rheumatoid arthritis, non-TNF biologic and targeted synthetic therapies demonstrated higher drug survival compared with TNF inhibitors over a 24-month follow-up period. Lack of effectiveness and adverse events were the main reasons for treatment discontinuation, highlighting the importance of selecting therapies based on both efficacy and tolerability.

Despite the small sample size, these findings suggest that drug survival is a valuable measure of long-term treatment performance in routine clinical practice. Incorporating drug retention data into clinical decision-making and pharmacoeconomic evaluations may improve patient outcomes and optimize resource utilization. Further studies with larger cohorts are warranted to confirm these preliminary observations and guide optimal therapy selection.

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