Treatment sequences and lines of therapy in rheumatoid arthritis: a real-world evaluation of retention and effectiveness

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Abstract

Objective

Many patients with rheumatoid arthritis (RA) do not maintain disease control or tolerance their first advanced therapy (AT), making subsequent treatment choices critical. This study described real-world patterns of sequential AT use and evaluate drug survival and effectiveness across multiple lines of therapy in a large Canadian RA cohort.

Methods

Adult RA patients from the Ontario Best Practice Research Initiative (OBRI) who initiated AT between 2008 and 2023 were included. Drug survival was defined as time from initiation to discontinuation. Effectiveness was assessed using changes in Clinical Disease Activity Index (CDAI), achievement of minimal clinically important difference (MCID), low disease activity (LDA), and remission at 6 months. Outcomes were compared before and after 2010, the year treat-to-target (T2T) guidelines were introduced. Analyses were adjusted using propensity scores and multiple imputation for missing data.

Results

Among 2,449 patients, TNFi agents were the most common first-line AT. Drug survival decreased with each subsequent line. Patients initiating AT after 2010 had shorter treatment durations (median 7.63 vs. 12.2 years), reflecting more frequent switching under T2T strategies. First-line therapies showed greater CDAI improvement and higher MCID, LDA, and remission rates. Effectiveness declined in later lines but remained clinically meaningful.

Conclusion

This study offers insights into real-world sequential AT use in Canadian RA care. First-line AT is associated with superior survival and effectiveness; however, subsequent therapies continue to provide important clinical benefits. These findings support the value of personalised sequential treatment strategies and highlight the need for further research to inform future RA management guidelines.

Key words

rheumatoid arthritis, retention, treatment sequence, effectiveness, advanced therapy

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Introduction

The management of rheumatoid arthritis (RA) is anchored in a treat-to-target strategy, emphasising regular assessment of disease activity and prompt adjustments in therapy to achieve remission or low disease activity. First-line treatment typically involves conventional synthetic DMARDs (csDMARDs), most often methotrexate (MTX). For patients who do not respond adequately to csDMARDs or who have poor prognostic features, treatment is escalated to biological (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) (1).

While practice guidelines outline when to initiate advanced therapies (AT), they do not provide strong direction on which agent to use first or how to sequence subsequent therapies after failure. In clinical practice, TNF inhibitors (TNFi) are often used as the initial AT. However, up to 60% of patients discontinue TNFi due to primary or secondary inefficacy or adverse events (2, 3). Multiple advanced therapies with differing mechanisms of action (MOA) are available, and although trials have demonstrated their efficacy in TNFi-experienced populations, the optimal sequencing of these agents remains unclear (4-7).

More importantly, real-world treatment decisions rarely follow a linear or uniform path. In day-to-day rheumatology practice, sequencing is shaped not only by clinical characteristics but also by comorbidities, medication tolerability, patient preferences, and reimbursement restrictions. As a result, treatment patterns in real-world care are highly heterogeneous and often diverge from guideline-based algorithms or clinical trial protocols.

Despite the central role of sequential therapy in RA management, there remains a critical evidence gap in understanding how patients are treated across multiple lines of AT in routine care. Real-world data on the effectiveness and durability of treatment across successive lines are essential for informing clinical decision-making, optimising long-term disease control, and aligning therapeutic choices with patient-centered care (8, 9).

The objective of this study was to examine real-world patterns of AT use across lines of therapy in Canadian RA patients enrolled in the Ontario Best Practices Research Initiative (OBRI) registry, and to evaluate how treatment retention and clinical effectiveness vary by line of therapy.

Methods

Data source

Established in 2008, the OBRI is a multicentre registry across Ontario, Canada, collecting data from rheumatologists and patients with RA at enrolment and follow-up, reflecting approximately one-third of the rheumatologists' practices in Ontario. Patients are eligible to be enrolled if they are ≥16 years of age at the time of diagnosis, ≥18 years of age at enrolment, have a rheumatologist-confirmed RA diagnosis, and have at least one swollen joint. Enrolled patients are interviewed every 6 months by phone and seen by their rheumatologist in routine care. Patients are asked for their general medical history and comorbidity status at enrolment. Rheumatologists also report any history of previous comorbidity, including cardiovascular disease and RA disease activity, such as inflammatory markers, patient global, physician global, and tender and swollen joint counts. Data on sociodemographics, smoking status, height, weight, and any prior and current medications are recorded during the rheumatologist's enrolment visit or the patient's interview. Patient-reported outcomes for functional status are also collected. At follow-up visits, all the information mentioned previously is updated. RA medication changes (including discontinuation and reasons for discontinuation) between visits are also captured. Rheumatologists report any incident of comorbidity and reassess disease activity during every follow-up visit.

For this study, patients who enrolled in the OBRI between January 1, 2008, and January 1, 2023, were included and categorised based on their line of therapy. Patients must also have had at least 6 months of follow-up visits to be included in the analysis.

Exposure

Recorded treatment exposures (drug name, start and stop dates) for the follow-

Table I. Baseline characteristics by Line of therapy for effectiveness analysis.

n=2449	Line 1	Line 2	Line 3	Line 4	Line 5	Line 6
Age (years)	n=1117	n=679	n=339	n=165	n=85	n=64
Mean ± SD	57.3 (12.6)	58.7 (11.9)	59.8 (11.5)	58.8 (10.4)	60.1 (9.8)	59.7 (10.7)
Female	n=1117	n=679	n=339	n=165	n=85	n=64
n (%)	882 (79.0)	572 (84.2)	287 (84.7)	143 (86.7)	75 (88.2)	62 (96.9)
Post-secondary education	n=1080	n=656	n=327	n=159	n=82	n=64
n (%)	629 (58.2)	396 (61.1)	215 (65.8)	105 (66.0)	52 (63.4)	39 (60.9)
Current smoker	n=644	n=301	n=138	n=66	n=33	n=10
n (%)	107 (16.6)	41 (13.6)	14 (10.1)	8 (12.1)	1 (3.03)	0 (0)
Annual household income >50,000 CAD	n=481	n=219	n=101	n=52	n=20	n=8
n (%)	275 (57.2)	119 (54.3)	55 (54.5)	30 (57.7)	11 (45.2)	4 (50.0)
Health insurance coverage, both private and public	n=642	n=300	n=138	n=66	n=33	n=10
n (%)	447 (69.6)	195 (65.0)	103 (74.6)	49 (74.2)	22 (66.7)	5 (50.0)
Disease duration (years)	n=1115	n=678	n=338	n=165	n=85	n=64
Mean ± SD	9.3 (9.4)	12.0 (9.7)	12.6 (9.4)	12.8 (9.2)	13.7 (9.1)	12.9 (5.6)
Positive RF (%)	n=1029	n=631	n=313	n=151	n=78	n=57
n (%)	777 (75.5)	467 (74.0)	223 (71.3)	103 (68.2)	49 (62.8)	33 (57.9)
HAQ-DI	n=891	n=425	n=182	n=75	n=35	n=16
Mean ± SD	1.30 (0.75)	1.40 (0.75)	1.50 (0.73)	1.52 (0.76)	1.74 (0.66)	1.68 (0.68)
RADAI	n=889	n=423	n=182	n=75	n=35	n=16
Mean ± SD	4.45 (2.11)	4.78 (2.23)	5.03 (2.26)	5.06 (2.26)	5.62 (2.26)	6.2 (2.20)
CDAI	n=1117	n=679	n=339	n=165	n=85	n=64
Mean ± SD	23.5 (12.7)	23.7 (13.0)	24.6 (12.7)	26.0 (12.1)	28.3 (13.4)	26.7 (13.5)
ESR	n=1043	n=640	n=324	n=160	n=83	n=64
Mean ± SD	24.5 (21.9)	23.1 (21.5)	24.6 (21.0)	27.9 (22.6)	28.0 (26.0)	27.7 (22.8)
CRP	n=1000	n=632	n=330	n=158	n=84	n=64
Mean ± SD	11.9 (19.2)	10.7 (18.9)	11.1 (18.6)	14.6 (22.5)	13.4 (28.7)	9.10 (11.8)
Comorbidity number	n=1117	n=837	n=338	n=165	n=85	n=64
Mean ± SD	0.39 (0.79)	0.40 (0.85)	0.23 (0.66)	0.22 (0.67)	0.25 (0.92)	0.08 (0.32)
csDMARD use	n=1117	n=679	n=339	n=165	n=85	n=64
n (%)	1025 (91.8)	526 (77.5)	254 (74.9)	121 (68.2)	58 (68.2)	41 (64.1)
Oral steroid use	n=1117	n=679	n=339	n=165	n=85	n=64
n (%)	293 (26.2)	221 (32.6)	139 (41.0)	77 (46.7)	45 (52.9)	40 (62.5)

ing AT were considered: TNFi: etanercept, adalimumab, infliximab, golimumab, and certolizumab; non-TNFi: abatacept, tocilizumab, rituximab, anakinra, and sarilumab; tsDMARDs: baricitinib, tofacitinib, and upadacitinib.

Line of therapy was defined as a treatment course under one drug name from start to stop date. Participants who started their AT before OBRI enrolment were included if they reported the AT start and stop dates. Patients at their first line of AT therapy was labelled as bio-naive patients.

Changing drugs in the same drug class (*e.g.* etanercept to adalimumab) was considered a new line of therapy while changing from originator to biosimilar drug brands, or *vice versa*, were considered the same line. Temporary stops of ≤90 days (180 days for rituximab) for the same biologics and ≤30 days for tsDMARDs were considered continuous use.

For treatment courses without a documented stop date, patients were assumed to have continued treatment until they initiated the subsequent drug, or to have remained on same the treatment until the end of follow-up.

Outcomes

The primary outcome was treatment discontinuation. Drug retention was defined as 'the length of time from initiation to discontinuation of therapy'. Patients were censored from the analysis at their last follow-up date if still on that drug at that time. Drug survival analysis used all available recorded lines of therapy including drugs used prior to OBRI enrolment. We did not apply any limitation on time between two consecutive lines of therapy.

We also evaluated effectiveness as a secondary outcome according to:

1. change in CDAI score between baseline and six months (or the nearest assessment to that date between 1 and 12 months) following treatment initiation, regardless of treatment discontinuation;
2. proportion of patients reaching the minimal clinically important difference (MCID) in CDAI scores at six months.

MCID cut points for improvement are: a) twelve for patients with a CDAI starting score in high disease activity (CDAI >22); b) six for patients starting in moderate disease activity (CDAI 10–22), and c) one for patients initially in low disease activity (CDAI <10) (10).

We also calculated CDAI low disease activity (CDAI ≤10) and remission (CDAI ≤2.8) rates at six months.

Statistical analysis

Descriptive statistics for all baseline characteristics were calculated as means and standard deviations (SD) for continuous variables and counts and proportions for categorical variables for each line of therapy. Since our aim was to describe actual treatment outcomes, we did not compare estimates statistically across different lines of therapy in the primary analyses.

- Primary analysis

We first evaluated time to treatment discontinuation due to any reason using Kaplan-Meier survival analysis (non-

parametric model) and Cox proportional hazards regression (HR) analysis (parametric models) for each line of therapy. For the analysis, we combined lines of therapies for more than 4 consecutive AT lines due to the small number of patients in these lines.

- Secondary analysis

To evaluate the effectiveness of each line of therapy, we used linear and logistic regression models, as appropriate, between baseline and six months of follow-up. We used the following covariates (*a priori* list of potential confounders) to adjust for confounding variables, in all multivariable regression models: line of therapy, baseline CDAI, RA disease duration, age, sex, drug class, number of comorbidities and RF status.

- Exploratory analysis

We compared outcomes in patients who initiated their first AT before and after 2010, the year treat-to-target guidelines were published. We also compared drug survival of the first AT in three therapeutic groups (TNFi, non-TNFi, tsDMARDs).

Multiple imputation, propensity scores

Multiple imputation was performed using the fully conditional specification method (FCS). Different methods are used to impute continuous and categorical variables. Twenty datasets were entered, and the results were combined using Rubin's rules (11-13).

Treatment attribution is not random and may rely on patients' specific factors. To balance predisposing factors that may increase a patient's likelihood of receiving treatment, a propensity score (PS) was calculated for each patient using baseline covariates differing between lines of therapy. The inverse probability of treatment weighting (IPTW) was generated to compare lines of therapy and applied to all regression models.

We combined multiple imputations with PS using a Within approach. In this approach, PS individually used to obtain treatment effect estimates in each imputation are combined to produce an overall estimate (14).

All analyses were completed using SAS 9.4 software (SAS Institute Inc. 2013. SAS/STAT® 13.1 User's Guide, Cary, NC).

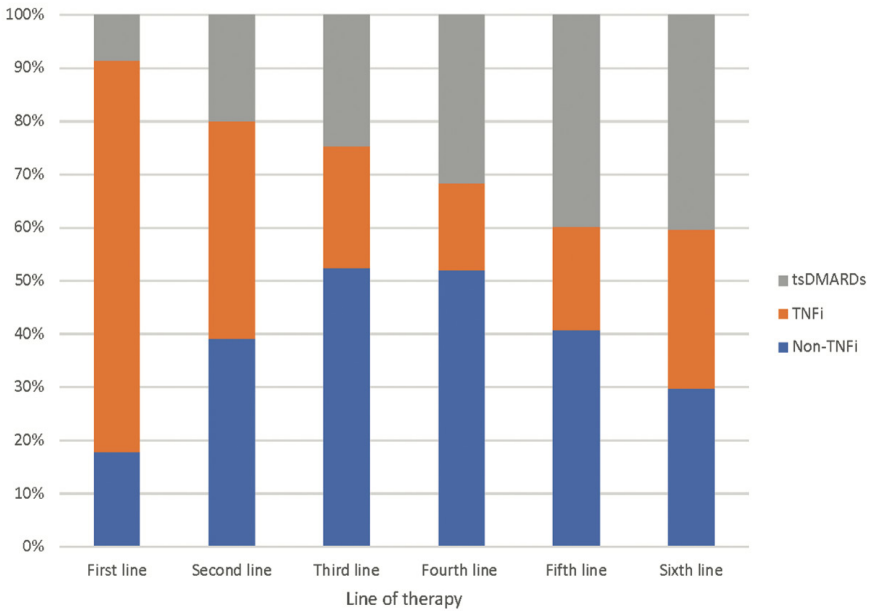

Fig. 1. Pattern of sequential therapy by drug class.

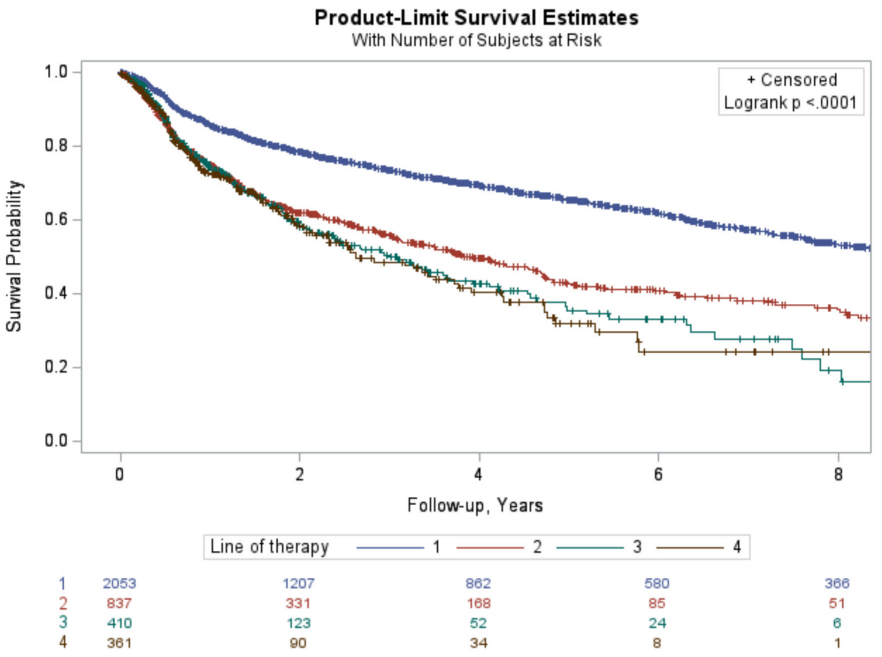

Fig. 2. Time to treatment discontinuation by line of therapy.

Results

A total of 3661 patients who started their first line of AT before or after enrolment were included (line one=2053, line two=837, line three=410, and lines four-to-six =361) (Supplementary Fig. S1). Table I shows the baseline characteristics of 2449 patients with available clinical data at the start of their AT (missing data are described in Suppl. Fig. S1). Most characteristics were similar across lines of therapy, except for a lower proportion of females and a higher percentage of current smokers for the first line of therapy. Compared to subsequent line of therapy (ranging from 12.0 to 13.7 years), patients in line one also had numerically lower disease duration (9.3 years). There was a numerically ascending trend for use

Table II. Time to treatment discontinuation by line of therapy performed on multiple imputation data (20 imputations), all and stratified by year of AT initiation.

Line of AT therapy	Mean survival (SE), years	Median survival (95% CI), years	Models weighted for PS (IPTW)	Models weighted for PS (IPTW) and adjusted for selected covariates *
			HRs (95% CI)	HRs (95% CI)
All patients				
Line 1	10.3 (0.29)	8.91 (8.13-9.69)	Ref	Ref
Line 2	5.10 (0.20)	3.92 (3.15-4.69)	**1.88 (1.81-1.95)**	**1.86 (1.78-1.95)**
Line 3	4.16 (0.27)	2.98 (2.34-3.93)	**2.12 (2.01-2.23)**	**2.07 (1.94-2.21)**
Line 4-6 combined	3.11 (0.15)	2.62 (2.07-3.76)	**2.24 (2.13-2.36)**	**2.07 (1.95-2.19)**
Patients initiated AT in 2010 or before				
Line 1	11.8 (0.41)	12.2 (9.75-13.7)	Ref	Ref
Line 2	4.98 (0.57)	3.83 (1.62-6.18)	**2.56 (2.26-2.89)**	**2.47 (2.22-2.74)**
Line 3	5.18 (1.29)	6.31 (0.43-10.0)	**2.29 (1.92-2.73)**	**2.12 (1.76-2.56)**
Patients initiated AT after 2010				
Line 1	4.47 (0.13)	7.63 (6.68-8.71)	Ref	Ref
Line 2	5.01 (0.20)	3.92 (3.15-4.69)	**1.65 (1.57-1.72)**	**1.65 (1.56-1.74)**
Line 3	3.79 (0.21)	2.93 (2.22-3.66)	**1.92 (1.80-2.04)**	**1.89 (1.78-2.01)**
Line 4-6 combined	3.11 (0.15)	2.62 (2.07-3.76)	**2.00 (1.90-2.12)**	**1.91 (1.80-2.02)**

*Adjusted for baseline characteristics (age, sex, disease duration, positive RF, CDAI, drug class, comorbidity number).

of steroids (26.2% to 62.5%) and descending trend for use of csDMARDs (91.8% to 64.1%) from line one to line six.

Type of AT treatment by line of therapy

Figure 1 shows the pattern of AT use by line of therapy. TNFi class was the most frequently used first line (74%) and second line (42%) AT, with etanercept and adalimumab being the first and second most common choices (Suppl. Fig. S2). The most common treatment in lines three and four was non-TNFi therapies, with abatacept, rituximab, and tocilizumab as the most common choices.

AT treatment discontinuation

Among 3661 patients, 1428 patients (39%) discontinued their AT treatment during follow-up. Compared to line one, the likelihood of discontinuation was significantly higher in line two, three and four-to-six combined (Fig. 2). The median survival time was 8.91 years (95% CI: 8.13–9.69) for the first line, 3.92 (95% CI: 3.15–4.69) for the second line, 2.98 (95% CI: 2.34–3.93) for the third line and 2.62 (95% CI: 2.07–3.76) for lines 4–6 combined (Table II). At year one, the probability of remaining on the first line drug was 85% (95% CI: 84–87%), 75% (95% CI: 72–77%) for the second line, 74% (95% CI: 69–79%) for the third line, and 73% (95% CI: 67–78%) for lines four-to-six combined (Suppl. Table S1).

Cox regression analysis weighting for PS (IPTW) and adjusting for baseline characteristics (age, sex, disease duration, positive RF, CDAI, drug class and comorbidity number) also confirmed higher discontinuation for the second line (adj HR: 1.86; 95% CI: 1.78–1.95), third line (adj HR: 2.07; 95% CI: 1.94–2.21), and fourth-to-sixth lines combined (adj HR: 2.07; 95% CI: 1.95–2.19) (Table II).

Compared to the first line, discontinuation of sequential lines of therapy was significantly higher both before and after 2010 (Table II). Pre- and post-2010 cohorts also displayed significant differences in first line AT retention, suggesting quicker switches post-2010 (median survival 12.2 *vs*. 7.63 years).

Comparing drug survival of the first AT in three therapeutic groups (TNFi, non-TNFi, tsDMARDs) showed that there was no significant difference in retention between these groups (Suppl. Fig. S3).

AT treatment effectiveness

Clinical data were available for 2085 patients at six-month follow-up. The mean (SD) change in CDAI between baseline and six months was 10.2 (13.3) for the first line, 6.96 (13.7) for the second line, 6.66 (12.9) for the third line and 6.33 (13.4) for lines four-to-six combined. A higher proportion of patients (57.4%) on their first line of therapy achieved a minimal clinically important difference compared to line two (43.5%), line three (40.4%) and lines four-to-six combined (39.9%). Fifty percent of patients achieved LDA and 13.4% achieved remission while on the first line. For remission and LDA, the proportion achieving these outcomes decreased linearly from line two through to lines four-to-six combined (Suppl. Table S2).

In regression analysis, weighting for PS (IPTW), compared to line one, other sequential lines had significantly lower reductions in CDAI between baseline and six months (Difference range: -3.17 to -3.42). Patients on their second line AT were less likely to achieve minimal clinically difference (OR: 0.57;95%CI: 0.55–0.59), LDA (OR: 0.59;95%CI: 0.57–0.62), and remission (OR: 0.61;95%CI: 0.57–0.65). There was a liner reduction in achieving MCID and LDA from lines one through to lines four-to-six combined (Table III).

The probability of reaching a MCID (adj ORs: 0.56; 95% CI: 0.54–0.59) and LDA (adj ORs: 0.58; 95% CI: 0.55–0.60) while on the second line of therapy remained significant after weighting for PS (IPTW) and adjusting for baseline characteristics. This was also true for line 3 and lines 4–6 combined (Table III).

Table III. Treatment effectiveness at 6 months by line of therapy, performed on multiple imputation data (20 imputations).

	CDAI change Difference (95% CI)	CDAI-MCID ORs (95% CI)	CDAI-LDA ORs (95% CI)	CDAI-remission ORs (95% CI)
Models weighted for PS (IPTW)				
Line of AT therapy				
Line 1	Ref	Ref	Ref	Ref
Line 2	-3.17 (-3.89, -2.46)	0.57 (0.55-0.59)	0.59 (0.57-0.62)	0.61 (0.57-0.65)
Line 3	-3.33 (-4.28, -2.39)	0.53 (0.50-0.56)	0.35 (0.33-0.37)	0.62 (0.56-0.69)
Line 4-6 combined	-3.42 (-4.48, -2.37)	0.49 (0.46-0.52)	0.31 (0.29-0.34)	0.28 (0.25, 0.32)
Models weighted for PS (IPTW) and adjusted for selected covariates *				
Line of AT therapy				
Line 1	Ref	Ref	Ref	Ref
Line 2	-3.57 (-4.15, -3.01)	0.56 (0.54-0.59)	0.58 (0.55-0.60)	0.61 (0.57-0.66)
Line 3	-4.05 (-4.82, -3.29)	0.51 (0.48-0.55)	0.35 (0.32-0.37)	0.74 (0.67-0.82)
Line 4-6 combined	-5.99 (-6.83, -5.14)	0.44 (0.40-0.47)	0.36 (0.33-0.40)	0.38 (0.33-0.44)

*Adjusted for baseline characteristics (age, sex, disease duration, positive RF, CDAI, drug class, comorbidity number).

Repeating analysis for patients who initiated their AT after 2010 showed consistent results in regression analysis after weighting for PS (IPTW) and adjusting for baseline characteristics (Suppl. Table S3).

Discussion

In this real-world study, we examined patterns of sequential AT use, drug survival, and treatment effectiveness among RA patients who received multiple lines of AT. Our findings indicate that TNFi agents were most commonly used as the first-line therapy. However, the use of non-TNFi biologics and tsDMARDs increased starting from the second line of treatment onward. This trend is consistent with our earlier work, which showed that non-TNFi use increased from 5.4% in 2008 to 33.8% in 2017 among RA patients (15). Similarly, Matsson *et al*. reported that TNFi therapies dominated as the first-line choice in a large US cohort, but subsequent treatment choices showed significant heterogeneity (16). Zhao *et al*. observed a comparable pattern in the British national registry, with increasing diversity in treatment selection beyond the first line (17). We also found that drug survival and treatment effectiveness were the highest among patients starting their first AT. In contrast, patients starting second- or later-line therapies experienced smaller improvements in CDAI. These results align with findings from a large registry study that demonstrated the greatest DAS28 improvements occurred with first-line biologic or small-molecule targeted agents (17). A systematic review of randomised clinical trials (RCTs) and observational studies similarly concluded that the efficacy of subsequent bDMARDs diminishes with each additional prior TNFi exposure (18).

Nonetheless, the type of first TNFi failure and the choice of second-line therapy may impact the effectiveness and persistence of subsequent treatment. For example, a recent study found that switching to a non-TNFi after initial TNFi failure resulted in better drug retention compared to switching to another TNFi (19). Another study showed that RA patients who experienced secondary failure to a first TNFi responded better to a second biologic, regardless of the MOA of the second agent (20).

Our study also suggests that treatment duration was shorter among patients who initiated therapy after 2010, likely reflecting more frequent switching due to the growing availability of newer advanced therapies, particularly non-TNFi agents. This finding aligns with observations from Zhao *et al*. (17). Leveraging our comprehensive database, we were able to examine drug use patterns across different modes of action. Among anti-TNF agents, etanercept emerged as the most commonly used first-line AT. Although TNFi therapies continued to be the predominant choice for second-line treatment, the gap between TNFi and non-TNFi biologic use was relatively small. Notably, we also found that drug survival in the first-line setting was independent of the specific medication used. A key strength of our study is the use of a large real-world database that captures clinical outcomes, patient-reported data, and treatment patterns, allowing for a robust assessment of drug survival and effectiveness. The long follow-up period enabled evaluation of evolving treatment trends shaped by changing guidelines and new therapies. To reduce bias, we used propensity score methods to balance covariates and applied multiple imputation for missing data. However, the study has limitations, including being limited to a single province with specific drug coverage policies, which may affect generalisability. Additionally, smaller sample sizes in later treatment lines may have constrained some analyses

In summary, our study provides novel real-world evidence from a Canadian cohort showing that TNFi continues to dominate as the preferred first-line advanced therapy in RA, consistent with patterns observed in US and UK cohorts. Importantly, we demonstrate that while first-line AT offers the greatest efficacy and drug survival, subsequent lines of therapy still yield meaningful clinical benefits – underscoring the value of sequential switching in achieving sustained disease control. This comprehensive evaluation of treatment patterns and outcomes across multiple lines of therapy adds important insights to the evolving RA treatment landscape. Future research with larger sample sizes and longer follow-up is needed to further explore treatment sequencing strategies and to support the refinement of clinical guidelines.

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