Seminars in Arthritis and Rheumatism 50 (2020) 915–922

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Discontinuation of biologic therapy due to lack/loss of response and adverse events is similar between TNFi and non-TNFi class: Results from a real-world rheumatoid arthritis cohort

Mohammad Movahedi[a,b], Elliot Hepworth[c], Reza Mirza[d], Angela Cesta[a], Maggie Larche[e], Claire Bombardier[a,f,g,*]

[a] Ontario Best Practices Research Initiative, Toronto General Research Institute, University Health Network, Toronto, ON, Canada
[b] Institute of Health Policy, Management, and Evaluation (IHPME), University of Toronto, Toronto, ON, Canada
[c] Division of Rheumatology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada
[d] Division of Rheumatology, Department of Medicine, University of Toronto, Toronto, ON, Canada
[e] Divisions of Rheumatology and Clinical Immunology and Allergy, Departments of Medicine and Pediatrics, McMaster University, Hamilton, ON, Canada
[f] Department of Medicine (DOM) and Institute of Health Policy, Management, and Evaluation (IHPME), University of Toronto, Toronto, ON, Canada
[g] Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada

ARTICLE INFO

Keywords:
Rheumatoid arthritis
Discontinuation
bDMARDs
Treatment
TNF

ABSTRACT

Objectives: Time to discontinuation of biologic therapy may be related to mechanism of action. We aimed to compare discontinuation of tumor necrosis factor inhibitors (TNFi) versus non-TNFi in an observational rheumatoid arthritis cohort.
Methods: Patients enrolled in the Ontario Best Practices Research Initiative (OBRI) starting biologic agents on or after 1st January 2010 were included. Time to discontinuation due to (1) any reason, (2) any of lack/loss of response, adverse events (AEs), physician, or patient decision, (3) lack/loss of response, and (4) AEs were assessed using Kaplan-Meier survival and Cox proportional hazards regression analysis.
Results: A total of 932 patients were included of whom 174 (18.7%) received non-TNFi and 758 (81.3%) received TNFi. Over a median follow-up of 1.7 years, discontinuation was reported for 416 (44.6%) due to any reason, 367 (39.4%) due to any of lack/loss of response, AEs, physician, or patient decision, 192 (20.6%) due to lack/loss of response, and 102 (10.9%) due to AEs. After adjusting for propensity score, there was no significant difference in discontinuation between the two classes due to any reason [HR 1.14 (0.90–1.46), $p = 0.28$], lack/loss of response [HR: 1.01 (0.70–1.47), $p = 0.95$], and AEs [HR: 1.06 (0.64–1.73), $p = 0.83$]. Similar results were found in biologic naïve patients.
Conclusions: This analysis demonstrates that discontinuation of therapy is similar in patients started on TNFi and non-TNFi therapies. There was also no significant difference in stopping due to lack/loss of response or AEs, suggesting that these reasons should not drive the selection of one treatment over another.

Introduction

Rheumatoid arthritis is an immune mediated systemic inflammatory disease typically affecting the synovial membrane but often has extra-articular manifestations [1,2]. The Ontario Best Practices Research Initiative (OBRI) is a province-wide Canadian database of over 3500 patients with active RA, many of whom are on biologic disease modifying anti-rheumatic drugs (DMARDs). Since patient recruitment into the OBRI registry started in 2008, there has been an explosion of novel drugs from a variety of classes that have demonstrated effectiveness at reducing disease activity and preventing negative outcomes [1,3]. The treat-to-target approach outlined in the 2012 CRA, 2015 ACR and 2016 EULAR guidelines for RA treatment suggest using a biologic DMARD (bDMARD) +/- conventional synthetic DMARD (csDMARD) in patients who fail to achieve low disease activity after a trial of single or combined csDMARD therapy for 3–6 month [1,4,5] . However, guidelines do not specify the order in which to initiate these therapies. As a result, rheumatologists select from an array of effective strategies.

The average annual rate of discontinuation for first bDMARD was reported as 17% for all biologic classes [6]. Most commonly, a tumor necrosis factor inhibitor (TNFi) with or without csDMARD is the initial biologic treatment after failure of combined csDMARD therapy

OBRI Investigators

* Corresponding author at: Ontario Best Practices Research Initiative, University Health Network, 200 Elizabeth St., 13 EN-224, Toronto, ON, Canada.
E-mail addresses: mmovahed@uhnresearch.ca (M. Movahedi), claire.bombardier@utoronto.ca (C. Bombardier).

https://doi.org/10.1016/j.semarthrit.2020.06.020
0049-0172/

[6,7] . Review of multiple RA databases reveal that within 6 months of initiating TNFi therapy, up to 23% of patients will discontinue therapy due to lack of efficacy [6,8].

Treatment retention (maintained, uninterrupted use of a single agent for treatment of RA) can be undermined by a variety of factors including 1° failure (never achieved response; lack of response), 2° failure (failure to maintain response after ≥ 3 months; loss of response), adverse events (AEs) and patient or physician decision [9]. Discontinuing, and switching between therapies may be time-consuming, unappreciated by patients and may delay finding tolerable and efficacious therapies for the patients [1,10].

Based on a review of the literature and to our best knowledge, this may be one of the first studies to thoroughly compare adjusted retention rates, stratified by reason for discontinuation, in TNFi and non-TNFi therapies, in RA patients with and without prior exposure to biologic therapy.

Methods

Study setting

The OBRI is a multicenter registry across Ontario, Canada incorporating rheumatologist assessments and a unique method of collecting data directly from the patients, using telephone interviewers. Patients in the OBRI are interviewed every six months. Rheumatologist assessments are conducted as per routine care. All patients have a rheumatologist confirmed diagnosis of RA with disease onset after 16 years of age and are 18 years of age or older at enrollment into the registry. Between January 2008 and January 2019, 3669 eligible patients across 65 sites gave their consent to participate in rheumatologist evaluations, and 3525 agreed to patient interviews.

Institutional ethics approval was obtained (REB# is 07–0729 AE), and informed consent was provided by all patients prior to study enrolment. This study was conducted in compliance with the principles of the Declaration of Helsinki.

Study population and data collection

For this study, we selected patients enrolled in OBRI (with at least one follow-up assessment) and initiated use of bDMARD therapy between January 2010 and January 2019. Patients were followed from bDMARD start until discontinuation/switching, death, lost to follow-up or last visit, whichever came first. The discontinuation date was defined as the first missed dose of therapy. Temporary stops of ≤ 180 days, after which the patients restarted the same bDMARD, were counted as continuous use.

Using a case report form, at each visit, physician report whether the current biologic medication is discontinued and, if so, they provide the reason for this discontinuation:(1) primary failure (lack of response), (2) secondary failure (failure to maintain response after 3 months- loss of response), 3) adverse event, 4) reimbursement issues, 5) patient decision, 6) physician decision, 7) improvement, 8) completed treatment, 9) dosage change, 10) pregnancy, 11) other. For this study dosage change was not considered as discontinuation.

Among the 3669 patients enrolled in OBRI, 1708 initiated a biologic agent at any time. From these, 932 initiated their first or a new biologic on or after 1st January 2010. These were included in the main analysis population (Fig. 1- study flowchart).

We chose to aggregate individual biologics by mechanism of action and only analyze the data as TNFi and non-TNFi groups because our sample size for several agents and classes were too small to generate sufficient power for individual analyses particularly for non-TNFi group (only 19%). A list of individual TNFi and non-TNFi has been provided in Supplementary; Table S1.

Statistical analysis

All analyses were conducted on the main analysis population. Descriptive statistics, specifically mean and standard deviation (SD) for continuous variables and counts and proportions for categorical variables, were produced for all baseline characteristics. Comparisons between patients on TNFi vs. non-TNFi were conducted using the independent-samples *t*-test for continuous variables and the chi-

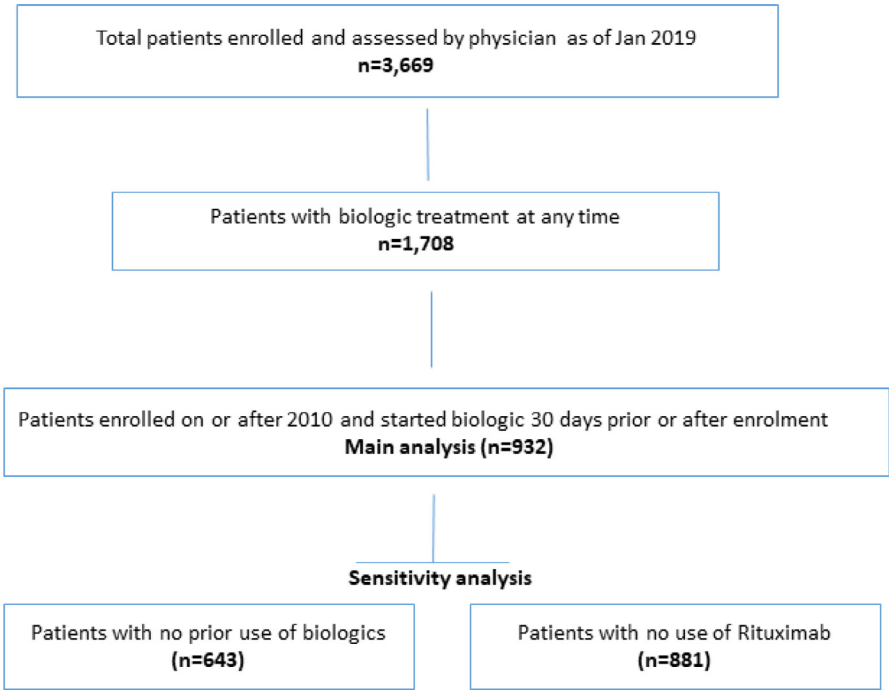

Fig. 1. Study Flow Chart.

square or the Fisher's Exact test for categorical variables. Time to discontinuation of bDMARD due to (1) any reason, (2) any of lack/loss of response, adverse events (AEs), physician, or patient decision, (3) lack/loss of response, and (4) AEs, were assessed using Kaplan-Meier survival analysis for non-TNFi versus TNFi users and Cox proportional hazards regression (HR) analysis.

To deal with missing data, Markov Chain Monte Carlo (MCMC) were used for multiple imputation assuming that all variables in the imputation model have a joint multivariable normal distribution (MVN). This model is commonly used under the assumption of missing at random (MAR). Twenty datasets were imputed and results were combined using Rubin's rules [11,12].

Estimating the propensity score

In observational studies, treatment effects are assessed by comparing the exposed and unexposed groups. The exposed group may be different from the unexposed group with respect to different factors (e.g. disease severity) other than treatment. Thus, direct comparisons of the 2 groups may be misleading and result in biased estimates of the treatment effect. In fact, propensity score analysis is used to simulate the process of random assignment when a randomization is not possible and observational data are already available. The propensity score (PS) is a balancing score that can be used to compare two groups and obtain an unbiased estimate [13,14]. In other words, by balancing treatment and control groups based on relevant characteristics, we can minimize or eliminate covariate effects on receipt of treatment to estimate the effect of treatment more accurately on an outcome. It, however, cannot balance non-measured variables between treatment groups in the way that randomization does.

For this study, using logistic regression, we estimated the PSs by modeling the main effect of the a priori list of potential confounders. Considered covariates at time of biologic initiation included: age, sex, disease duration, education, annual household income, health insurance coverage, smoking status, rheumatoid factor (RF), ESR, CDAI, HAQ-DI, fatigue, the presence of comorbidity, prior use of bDMARDs, csDMARDs, concomitant use of csDMARDs, steroids, NSAIDs, and the year of bDMARDs initiation (Table 1).

All variables except sex, education, and RF were assessed at each visit. Thus, a time window of 60 days was applied to capture the earliest or the most recent disease activity assessment of patients at their biologic initiation. For annual household income, smoking status, health insurance coverage and comorbidity profile this time window was one year.

Propensity score implementation and discontinuation estimation

We compared rates of discontinuation in non-TNFi versus TNFi users with Cox proportional hazard regression models and results were presented as hazard ratios (HR) and 95% confidence intervals (CI).

We estimated the treatment effect using PS weighting including the stabilized inverse probability of treatment weight (IPTW). Stabilized weights are used to reduce variance of the estimated treatment effect [15]. The estimated weights were incorporated into a Cox regression model that only included the treatment variable. We repeated our analysis for patients on the "common area of support", that is restricted to the range of PSs at which we observe both treated and untreated patients.

We also conducted analysis using a PSs stratification (quantiles) approach, which has been shown to remove up to 90% of the bias in the unadjusted estimate [16]. We then simply added the indicator variables for strata to the Cox regression model for estimating treatment effect. We combined multiple imputation with propensity score using a within approach. In this approach, PSs individually used to obtain treatment effect estimates in each imputation, are combined to produce an overall estimate [17]. To create an IPTW adjusted survival curve, we applied a SAS Macro to one imputed dataset [18].

Propensity score evaluation

To assess the quality of the propensity scores estimated we used two approaches: 1) The good of fitness for multivariable logistic model was assessed using a Hosmer-Lemeshow test. 2) We also compared the distribution of PSs across the treatment within strata (quantiles).

Sensitivity analysis

We conducted two sensitivity analyses comparing discontinuation between non-TNFi and TNFi by excluding: 1) patients with prior exposure to biologic (not Naïve) before enrolment; 2) patients starting Rituximab, given gaps of 180 days in treatment are not unusual, and therefore may affect the accuracy of the stop date (Fig. 1).

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient socio-demographics and clinical characteristics

Overall study population

932 patients started a biologic on or after 1st January 2010 (Fig. 1), among whom 758 (81.3%) were being treated with TNFi and the remaining 174 (18.7%) with non-TNFi therapy. The average age (SD) of the total cohort was 56.7 (12.9) years, with most patients being female (n = 741; 79.5%). One hundred forty-nine patients were current smokers (16.7%). At baseline, the mean (SD) duration of RA in the total cohort was 9.0 (9.3) years, with most patients being RF positive (n = 650; 75.3%). Mean (SD) CDAI was 24.0 (12.6) and HAQ-DI was 1.3 (0.8). Thirty-one percent of patients had a prior exposure to bDMARDs (not Naïve) prior to enrolment into the OBRI. The number of patients on concurrent csDMARDs was 819 (87.9%) (Table 1).

TNFi vs. non-TNFi therapy

Key differences in patient socio-demographics, disease and medication profiles based on type of therapy (TNFi vs. non-TNFi) are summarized in Table 1. Patients treated with non-TNFi were less likely to be current smokers (9.4% vs. 18.4%, p = 0.007). No other significant sociodemographic differences were observed between groups.

With respect to clinical and medication profiles, patients treated with non-TNFi were more likely to have longer mean disease duration (11.7 vs. 8.4 years; $p<0.001$), more likely to be exposed to a prior bDMARDs before their enrolment (54.6% vs. 25.6%, $p<0.001$) and less likely to be treated with a concurrent csDMARD (78.7% vs. 90.0%; $p<0.001$), compared to those treated with TNFi (Table 1). Furthermore, at baseline, patients on non-TNFi had significantly higher disease activity, as indicated by the higher mean CDAI (25.9 vs. 23.6; p = 0.076) and HAQ-DI (1.5 vs. 1.2; $p<0.001$), and had a higher prevalence of certain comorbidities (e.g. cancer, lung diseases and infection).

Evaluation of propensity score

Hosmer-Lemeshow test was not significant (p = 0.45) showing that the logistic regression model fit our data well. In addition, distribution of propensity score across treatment group within quantile was very similar (Supplementary; Figure S1).

Table 1
Baseline Characteristics of Patients; Overall and by Mechanism of Action.

Variables	Biologic by mechanism of action			P Value
	Total (*N* = 932)	TNFi (*N* = 758)	non-TNFi (*N* = 174)	
Sociodemographic profile				
Gender, Female, n (%) [α]	741 (79.5)	602 (79.4)	139 (79.9)	*0.891*
Age at start of medication [α]				*0.134*
Mean ± SD	56.7 ± 12.9	56.4 ± 12.8	58.0 ± 13.1	
Weight in kg [α]				*0.661*
N≠	844	686	158	
Mean ± SD	74.0 ± 20.6	73.8 ± 20.6	74.6 ± 20.8	
Marital status				*0.921*
N≠	902	731	171	
Married, n (%)	609 (67.5)	493 (67.4)	116 (67.8)	
Education status [α]				*0.169*
N≠	902	731	171	
Post-secondary, n (%)	533 (59.1)	424 (58.0)	109 (63.7)	
Annual household income [α]				*0.608*
N≠	734	591	143	
> 50,000 CAD, n (%)	412 (56.1)	329 (55.7)	83 (58.0)	
Health insurance coverage [α]				*0.386*
N≠	888	719	169	
Public (OHIP) + private or ODB (%)	709 (79.8)	570 (79.3)	139 (82.2)	
Smoking status [α]				***0.007***
N≠	893	723	170	
Never, n (%)	421 (47.1)	341 (47.2)	80 (47.1)	
Past, n (%)	323 (36.2)	249 (34.4)	74 (43.5)	
Current, n (%)	149 (16.7)	133 (18.4)	16 (9.4)	
Clinical profile				
Disease duration at start of medication [α]				<***0.001***
N≠	931	757	174	
Mean ± SD	9.0 ± 9.3	8.4 ± 8.7	11.7 ± 11.2	
RF [α]				*0.503*
N≠	863	710	153	
Positive, n (%)	50 (75.3)	538 (75.8)	112 (73.2)	
ESR (mm/hr.) [α]				*0.759*
N≠	715	580	135	
Mean ± SD	22.7 ± 20.9	22.8 ± 20.6	22.2 ± 22.4	
CRP (mg/L)				*0.633*
N≠	684	560	124	
Mean ± SD	11.4 ± 18.3	11.2 ± 17.7	12.1 ± 20.7	
PtGA				*0.539*
N≠	707	581	126	
Mean ± SD	5.4 ± 2.7	5.4 ± 2.7	5.5 ± 2.8	
PhGA				*0.511*
N≠	655	538	117	
Mean ± SD	4.9 ± 2.3	4.9 ± 2.3	5.1 ± 2.6	
28SJC				***0.025***
N≠	808	665	143	
Mean ± SD	6.5 ± 4.6	6.3 ± 4.5	7.3 ± 5.3	
28TJC				*0.253*
N≠	783	651	132	
Mean ± SD	6.9 ± 6.3	6.8 ± 6.1	7.5 ± 7.1	
CDAI [α]				*0.076*
N≠	702	583	119	
Mean ± SD	24.0 ± 12.6	23.6 ± 12.1	25.9 ± 14.7	
DAS28-ESR				*0.811*
N≠	713	593	120	
Mean ± SD	4.6 ± 1.4	4.6 ± 1.4	4.6 ± 1.6	
HAQ-DI [α]				<***0.001***
N≠	739	594	145	
Mean ± SD	1.3 ± 0.8	1.2 ± 0.8	1.5 ± 0.8	
HAQ-Pain				***0.002***
N≠	739	594	145	
Mean ± SD	1.6 ± 0.8	1.6 ± 0.8	1.8 ± 0.8	
Fatigue score [α]				***0.002***
N	645	519	126	
Mean ± SD	5.4 ± 3.0	5.3 ± 3.1	6.2 ± 2.7	
Comorbidity profile				
Presence of main comorbidity				*0.116*
Yes, n (%)	491 (52.7)	390 (51.5)	101 (58.0)	
Number of main comorbidities				***0.031***
Mean ± SD	1.6 ± 2.0	1.5 ± 1.9	1.9 ± 2.2	
Hypertension				*0.913*
Yes, n (%)	222 (23.8)	180 (23.7)	42 (24.1)	
Cardiovascular disease				*0.566*
Yes, n (%)	96 (10.3)	76 (10.0)	20 (11.5)	

(*continued*)

Table 1 (*Continued*)

Variables	Biologic by mechanism of action			P Value
	Total (*N* = 932)	TNFi (*N* = 758)	non-TNFi (*N* = 174)	
Diabetes Mellitus				*0.936*
Yes, n (%)	71 (7.6)	58 (7.7)	13 (7.5)	
Lung disease $^{\alpha}$				***0.027***
Yes, n (%)	92 (9.9)	67 (8.8)	25 (14.4)	
Tuberculosis, Pneumonia, Serious infection $^{\alpha}$				***0.044***
Yes, n (%)	204 (21.9)	156 (20.6)	48 (27.6)	
Kidney disease				*1.000* †
Yes, n (%)	20 (2.1)	16 (2.1)	4 (2.3)	
GI and liver disease				*0.565*
Yes, n (%)	137 (14.7)	109 (14.4)	28 (16.1)	
Cancer disease $^{\alpha}$				***<0.001***
Yes, n (%)	54 (5.8)	34 (4.5)	20 (11.5)	
Depression disease				*0.713*
Yes, n (%)	173 (18.6)	139 (18.3)	34 (19.5)	
Osteo or degenerative $^{\alpha}$ **arthritis**				***0.005***
Yes, n (%)	228 (24.5)	171 (22.6)	57 (32.8)	
Medication profile				
Prior use of csDMARDs $^{\alpha}$				***0.005***
N$^{\neq}$	927	753	174	
Yes, n (%)	823 (88.8)	658 (87.4)	165 (94.8)	
Prior use of bDMARDs $^{\alpha}$				***<0.001***
Yes, n (%)	289 (31.0)	194 (25.6)	95 (54.6)	
Concomitant use of csDMARDs $^{\alpha}$				***<0.001***
Yes, n (%)	819 (87.9)	682 (90.0)	137 (78.7)	
Concomitant use of NSAIDs $^{\alpha}$				*0.058*
Yes, n (%)	223 (23.9)	191 (25.2)	32 (18.4)	
Concomitant use of steroids $^{\alpha}$				***<0.001***
Yes, n (%)	220 (23.6)	161 (21.2)	59 (33.9)	
Year of use of bDMARD $^{\alpha}$				*0.29*
2010, n (%)	60 (6.4)	49 (6.5)	11 (6.3)	
2011, n (%)	173 (18.6)	149 (19.7)	24 (13.8)	
2012, n (%)	166 (17.8)	139 (18.3)	27 (15.5)	
2013, n (%)	125 (13.4)	99 (13.1)	26 (14.9)	
2014, n (%)	115 (12.3)	93 (12.3)	22 (12.6)	
2015, n (%)	102 (10.9)	78 (10.3)	24 (13.8)	
2016, n (%)	92 (9.9)	68 (9.0)	24 (13.8)	
2017, n (%)	61 (6.6)	53 (7.0)	8 (4.6)	
2018, n (%)	38 (4.1)	30 (4.0)	8 (4.6)	
†Exact test				

$^{\neq}$ Number of available data (N) was presented when the complete data were not available.
Bold: Statistically significant p-values < 0.05.
OHIP: Ontario health insurance program; ODB: Ontario drug benefit; CDAI: clinical disease activity index; HAQ-DI: health assessment questionnaire disability index; bDMARDs: biologic disease modifying antirheumatic drugs; csDMARDs: conventional synthetic disease modifying antirheumatic drugs; RF: rheumatoid factor; ESR: Erythrocyte sedimentation rate; SD=standard deviation; N/*A*=not applicable$^{\neq}$.

Impact of mechanism of action of therapy on time to bDMARD discontinuation

Over a median follow-up of 1.7 years (survival mean: 2.4 years), bDMARD discontinuation was reported for 416 (44.6%) due to any reason giving an incidence of 18.4 per 100 person–years (Table 2), 367 (39.4%) due to any of lack/loss of response, AEs, physician, or patient decision (incidence of 16.3 per 100 person–years), 192 (20.6%) due to lack/loss of response (incidence of 8.5 per 100 person–years), and 102 (10.9%) due to AEs (incidence of 4.5 per 100 person–years) (Table 2). A total of 327 discontinuations due to any reason were identified in patients exposed to TNFi therapy (incidence of 17.4 per 100 person–years), and 89 cases were identified in those exposed to non-TNFi therapy (incidence of 23.7 per 100 person–years).

Time to bDMARD discontinuation by mechanism of action multivariable cox regression

In univariable survival analysis, patients starting non-TNFi therapy had a higher discontinuation due to any reason (unadjusted HR=1.33 (95% CI: 1.05–1.68) compared to patients starting TNFi therapy (Table 3).

Fig. 2 depicts the time to bDMARD discontinuation by mechanism of action of therapy. After using the propensity score weighted (IPTW) model, no significant differences were observed in terms of discontinuation due to any reason (Fig. 2a; $p = 0.71$), due to any of lack/loss of response, AEs, physician, or patient decision (combined) (Fig. 2b; $p = 0.96$), due to lack/loss of response (Fig. 2c; $p = 0.98$), and due to AEs (Fig. 2d; $p = 0.90$).

Upon adjustment for stabilized IPTW and stratification (quantiles) across 20 multiple imputed datasets, all resulted in reduced HRs compared to the unadjusted estimate, as shown in the Table 3 (stabilized IPTW: HR=1.14 (95% CI: 0.90–1.46); stratification: HR=1.10 (95% CI: 0.84–1.43)).

In addition, no significant association was observed for discontinuation due to specific reasons including due to lack/loss of response (stabilized IPTW: HR =1.01(95% CI: 0.70–1.47); stratification: HR=1.04 (95% CI: 0.70–1.54)) and due to AEs (stabilized IPTW: HR =1.06 (95% CI: 0.64–1.73); stratification: HR=0.82 (95% CI: 0.48–1.40)) (Table 3).

Repeating analysis for stabilized IPTW restricting patients with area of common support did not change the magnitude of the results (Supplementary; Table S2).

Table 2
Observation Time and Incidence of Discontinuation by Reason and Mechanism of Action .

	Overall (n = 932)	TNFi (n = 758)	non-TNFi (n = 174)
Total Person-years	**2258.03**	**1881.4**	**376.6**
Any reason			
Event	416	327	89
Incidence rate per 100 person-years (95%CI)	18.4 (16.7–20.3)	17.4 (15.6–19.4)	23.7 (19.2–29.1)
Any of lack/loss of response, adverse events, physician's, and patient's decision			
Event	367	295	72
Incidence rate per 100 person-years (95%CI)	16.3 (14.7–18.0)	15.7 (14.0–17.6)	19.1 (15.2–24.1)
Lack/loss of response			
Event	192	154	38
Incidence rate per 100 person-years (95%CI)	8.5 (7.4–9.8)	8.2 (7.0–9.6)	10.1 (7.3–13.9)
Adverse events			
Event	102	82	20
Incidence rate per 100 person-years (95%CI)	4.5 (3.7–5.5)	4.4 (3.5–5.4)	5.3 (3.4–8.2)

Sensitivity analysis

Repeating the multivariable analysis for patients with no prior exposure to bDMARDs therapy did not change the results when comparing discontinuation between non-TNFi and TNFi therapy (Supplementary; Table S3). Similar results were also observed after excluding patients with Rituximab therapy (Supplementary; Table S4).

Table 3
Discontinuation of TNFi vs. non-TNFi by Reason for Discontinuation – Multivariable Cox Regression.

Reason for Discontinuation N = 932	non-TNFi vs. TNFi HRs (95% CI)		
	Unadjusted	Stabilized IPTW	Stratification
Any reason	**1.33 (1.05–1.68), 0.02**	1.14 (0.90–1.46), 0.28	1.10 (0.84–1.43), 0.48
Any of 1°/2° failure, AEs, physician, or patient's decision	1.18 (0.91–1.53), 0.20	1.05 (0.80–1.36), 0.74	0.97 (0.73–1.29), 0.84
Lack/loss of response	1.19 (0.84–1.70), 0.33	1.01 (0.70–1.47), 0.95	1.04 (0.70–1.54), 0.85
AEs	1.17 (0.71–1.90), 0.54	1.06 (0.64–1.73), 0.83	0.82 (0.48–1.40), 0.47

AEs=adverse events, TNFi=tumor necrosis factor inhibitor, IPTW: inverse probability of treatment weight.
Bold: Statistically significant p-value.

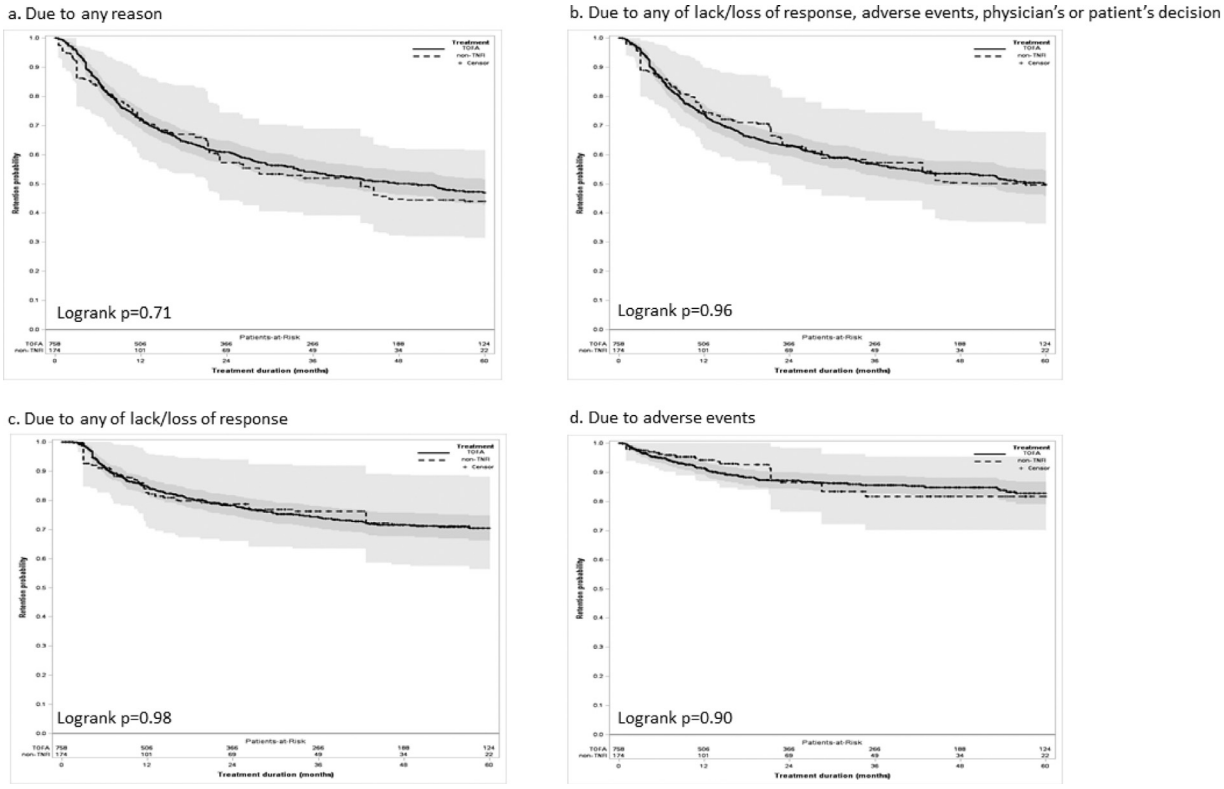

Fig. 2. Stabilized Propensity Score Weighted (IPTW) Survival Curves for Time to Discontinuation of bDMARD Based on Mechanism of Action.

Discussion

This real-world observational study directly compares drug survival in patients with RA initiating a TNFi versus a non-TNFi, stratified by reason for discontinuation. The results of our study suggest that, after adjusting for differences in baseline characteristics, RA patients started on TNFi agents have similar drug survival compared to other bDMARDs when assessing all reasons for discontinuation, and individual reasons for discontinuation. Similar results were also observed for biologic-naïve patients. Once, through the use of propensity score weighted adjustment, the factors that made the non-TNFi group more likely to discontinue therapy were balanced, the unadjusted difference in drug survival between groups was abolished. This suggests that differences in drug survival seen in rheumatology practice may be driven to a greater extent by patient characteristics than by differences in drug class.

Compared to similar studies, this analysis included considerably more patients being started on non-TNFi (19%). For example, Ramiro et al. had only 2.5% starting non-TNFi therapy (6). This relative paucity of non-TNFi use as advanced therapy likely occurs because older guidelines recommended universally starting with TNFi and also due to the relative longevity of market presence experienced by the TNFi class [19].

Our study population was quite comparable in terms of age, use of csDMARDs, disease severity, and differences between those started on TNFi versus non-TNFi. The patients starting non-TNFi therapies were slightly older (58.0 years) compared to the TNFi group (56.7 years) and similarly reported in other studies such as Ramiro et al. (65.3 vs. 59.6), Favalli et al. (tocilizumab 58.2, TNFi 53.7) and Frisell et al. (tocilizumab 58.1, abatacept 60.8, rituximab 64.9, TNFi 55.3) [6,20,21]. The non-TNFi group in our study were less likely to be treated with csDMARDs compared to the TNFi group. This difference was also demonstrated in the Frisell et al. study [21] but not in the Ramiro et al. study and the Choquette et al. abstract [6,22]. Evidence supporting relative efficacy of tocilizumab over adalimumab when used as monotherapy may contribute to relatively higher utilization of non-TNFi therapies in those not taking methotrexate due to adverse effect or other reasons [23]. The higher disease severity (CDAI, HAQ-DI) and higher percentage of some comorbidities at baseline seen in our study's non-TNFi group was also demonstrated in Frisell et al. study [21].

This analysis reports a 74% retention rate at one year, on all biologics (75% TNFi, 67% non-TNF), which is comparable to the findings of a meta-analysis completed by Souto et al. [24]. Frisell et al. [21] also reported that by year one 30% of patients discontinued their TNFi. The median biologic survival in our study was 1.7 years per patient. Compared to our study, Ramiro et al. [6] in a large cohort (2281 and 1097 first and second bDMARDs users) reported a longer median survival time of 4.1 and 3.3 years in first and second biologics, respectively.

Based on our adjusted analysis, patients who started their biological agent had similar drug survival, for any reason, regardless of whether they were started on TNFi agents or non-TNFi agents. Ramiro et al. [6] showed that after adjusting for propensity score, TNFi class had lower discontinuation rates than non-TNFi for first and second bDMARDs. However, they did not include anakinra in the non-TNFi class, which may account for the different results from our study. In contrast, Frisell et al. [21] showed that individual non-TNFi, particularly tocilizumab and rituximab, had longer retention and higher effectiveness than the TNFi class. Lauper et al. [24] also showed that compared with TNFi, tocilizumab had longer retention and similar effectiveness in patients with inadequate response to at least one bDMARD. Gottenberg et al. [25] compared retention of three non-TNFi; rituximab, abatacept and tocilizumab in patients with inadequate response to at least one TNFi. However, we are not able to compare our results directly with these studies because of differences in study design and inclusion criteria. Moreover, the low number of individual non-TNFi users in our study did not allow us to run analyses comparing individual non-TNFi therapies with the TNFi class.

In this study, we compared bDMARD discontinuation due to AEs or lack/loss of response. We were not able to find other studies that compared two biologic classes by discontinuation reason and therefore cannot comment on whether the lack of significance in discontinuation due to AEs or lack/loss of response between treatment groups has been replicated. The only other study that has compared biologic agents stratified by reason for discontinuation did so comparing individual TNFi's [9].

Strengths of our study include the use of multicenter data, controlling for disease severity, comorbidities, and demographics to balance measured prognostic factors by adjusting our models for propensity score. Our database had excellent follow-up duration, averaging two years, and included patients with up to 8 years of follow-up. Additionally, we had a relatively large sample size of patients starting non-TNFi's.

We did use two different propensity score adjustment approaches for treatment effect which gave similar results. However, given lack of randomization, the estimates might be biased due to some unmeasured confounders.

There are several limitations of this study. First, given its observational nature there are unmeasured patient and physician variables that cannot be reliably accounted for. This limitation is partially addressed given that we adjusted for age, sex, income, severity of disease and other factors that are commonly different between those utilizing TNFi vs. non-TNFi. We also had a small number of patients in the non-TNFi group, which precludes us from identifying whether any specific non-TNFi drug may have differing survival rates as compared to the TNFi group. Additionally, there are likely systematic differences in the practice patterns of physicians participating in OBRI.

In summary, this study demonstrates that discontinuation of therapy is similar in patients started on TNFi and non-TNFi therapies. Between groups, there was no significant difference in discontinuation due to lack/loss of response or AEs, suggesting that the reason for discontinuation may be independent of drug class.

Funding

No funding has been provided for this manuscript. The OBRI registry is funded by peer reviewed grants from CIHR (Canadian Institute for Health Research), Ontario Ministry of Health and Long-Term Care (MOHLTC), Canadian Arthritis Network (CAN) and unrestricted grants from: AbbVie, Amgen, Janssen, Merck, Novartis, and Pfizer.

Ethics

All sites had ethics approval to enroll patients. All patients signed informed consent. Ethics approval: REB# is 07–0729 AE (University Health Network).

Contributorship

All authors contributed to the conception or design of the work, revised the work critically and approved the final version of the manuscript. MM conducted the data analysis. MM and EH drafted the manuscript.

Declaration of Competing Interest

MM, AC are employees at OBRI with no conflict of interest. EH and RM are rheumatology fellows at the University of Ottawa and University of Toronto respectively with no conflict of interest, ML is an associate professor in McMaster university and has no conflict of interest.

CB held a Canada Research Chair in Knowledge Transfer for Musculoskeletal Care.

Acknowledgment

We would like to thank all OBRI participants and the following investigators:

Drs. Ahluwalia, V., Ahmad, Z., Akhavan, P., Albert, L., Alderdice, C., Aubrey, M., Aydin, S., Bajaj, S., Bell, M., Bensen, W., Bhavsar, S., Bobba, R., Bombardier, C., Bookman, A., Brophy, J., Cabral, A., Carette, S., Carmona, R., Chow, A., Choy, G., Ciaschini, P., Cividino, A., Cohen, D., Dixit, S., Faraawi, R., Haaland, D., Hanna, B., Haroon, N., Hochman, J., Jaroszynska, A., Johnson, S., Joshi, R., Kagal, A., Karasik, A., Karsh, J., Keystone, E., Khalidi, N., Kuriya, B., Lake, S., Larche, M., Lau, A., LeRiche, N., Leung, Fe., Leung, Fr., Mahendira, D., Matsos, M., McDonald-Blumer, H., McKeown, E., Midzic, I., Milman, N., Mittoo, S., Mody, A., Montgomery, A., Mulgund, M., Ng, E., Papneja, T., Pavlova, P., Perlin, L., Pope, J., Purvis, J., Rai, R., Rohekar, G., Rohekar, S., Ruban, T., Samadi, N., Sandhu, S., Shaikh, S., Shickh, A., Shupak, R., Smith, D., Soucy, E., Stein, J., Thompson, A., Thorne, C., Wilkinson, S.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2020.06.020.

References

[1] Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76(6):960–77.
[2] Widdifield J, Paterson JM, Bernatsky S, Tu K, Tomlinson G, Kuriya B, et al. The epidemiology of rheumatoid arthritis in Ontario, Canada. Arthritis Rheumatol 2014. p. 786–93.
[3] Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. Lancet 2017. p. 2338–48.
[4] Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol 2012;39(8):1559–82.
[5] Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2015 2015/11/06 ed2016. p. 1-26.
[6] Ramiro SRL, van der Heijde D, Harrison D, Collier D, Michaud K. Discontinuation rates of biologics in patients with rheumatoid arthritis: are TNF inhibitors different from non-TNF inhibitors? RMD Open 2015:e000155 11/18 ed2015.
[7] O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 369 (4):307–18.
[8] Curtis JR, Jain A, Askling J, Bridges SL, Carmona L, Dixon W, et al. A comparison of patient characteristics and outcomes in selected European and U.S. rheumatoid arthritis registries. Semin Arthritis Rheum 2010. p. 2–14.e1.
[9] Du Pan SM, Dehler S, Ciurea A, Ziswiler HR, Gabay C, Finckh A, et al. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum 2009. p. 560–8.
[10] Wolfe F, Michaud K. Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. Arthritis Rheum 2007. p. 2135–42.
[11] Rubin D. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons; 1987.
[12] van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999. p. 681–94.
[13] D'Agostino RB. Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17(19):2265–81.
[14] Rai SN, Wu X, Srivastava DK, Craycroft JA, Rai JP, Srivastava S, et al. Review: propensity score methods with application to the HELP clinic clinical study. Open Access Med Stat 2018;8:11–23.
[15] Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34(28):3661–79.
[16] Cochran WG. The effectiveness of adjustment by subclassification in removing bias in observational studies. Biometrics 1968;24(2):295–313.
[17] Granger E, Sergeant JC, Lunt M. Avoiding pitfalls when combining multiple imputation and propensity scores. Stat Med 2019;38(26):5120–32.
[18] Meyers JP. The%NewSURV family of macros: an update on the survival plotting macro %NewSURV and an introduction to expansion macros. In: Proceeding of Pharmaceutical SAS Users Group Conference (PharmaSUG 2017) Paper DV15 Carry. NC: SAS Institute Inc; 2017.
[19] Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008. p. 762–84.
[20] Favalli E BM, Puttini PS, et al. FRI0215 Comparative efficacy and retention rate of tocilizumab and tnf inhibitors used in combination with methotrexate as first-line biologic therapy in rheumatoid arthritis: data from a multicentre observational registry. Ann Rheum Dis 2017;76:5642017.
[21] Frisell T, Dehlin M, Di Giuseppe D, Feltelius N, Turesson C, Askling J. Comparative effectiveness of abatacept, rituximab, tocilizumab and TNFi biologics in RA: results from the nationwide Swedish register. Rheumatology (Oxford) 2019.
[22] Choquette D BL, Alemao E, et al. FRI0230 Retention rates of tnf inhibitors and abatacept used as a first biologic dmard in the treatment of rheumatoid arthritis: 8 years of experience from the rhumadata® registry. Ann Rheum Dis 2017;76:571–2 2017.
[23] Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013:1541–50 03/18 ed2013.
[24] Lauper K, Nordstrom DC, Pavelka K, Hernandez MV, Kvien TK, Kristianslund EK, et al. Comparative effectiveness of tocilizumab versus TNF inhibitors as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis after the use of at least one biologic disease-modifying antirheumatic drug: analyses from the pan-European TOCERRA register collaboration. Ann Rheum Dis 2018;77(9):1276–82.
[25] Gottenberg JE, Morel J, Perrodeau E, Bardin T, Combe B, Dougados M, et al. Comparative effectiveness of rituximab, abatacept, and tocilizumab in adults with rheumatoid arthritis and inadequate response to TNF inhibitors: prospective cohort study. BMJ (Clin Res ed.) 2019;364:l67.