

Physician- and Patient-reported Effectiveness Are Similar for Tofacitinib and TNFi in Rheumatoid Arthritis: Data From a Rheumatoid Arthritis Registry

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ABSTRACT. *Objective.* Tofacitinib (TOF) is an oral, small-molecule drug used for rheumatoid arthritis (RA) treatment and is one of several alternative treatments to tumor necrosis factor inhibitors (TNFi). We evaluated physician- and patient-reported effectiveness of TNFi compared to TOF, using real-world data from the Ontario Best Practices Research Initiative (OBRI).

Methods. Patients enrolled in the OBRI initiating TOF or TNFi between 2014 and 2019 were included. Patients were required to have physician- and patient-reported effectiveness outcome data, including Clinical Disease Activity Index (CDAI) and RA Disease Activity Index (RADAI), available at treatment initiation and 6 (\pm 2) months later. To deal with confounding by indication, we estimated propensity scores (PS) for covariates.

Results. Four hundred nineteen patients were included. Of those, 226 initiated a TNFi and 193 TOF, and had a mean (SD) disease duration of 8.0 (8.7) and 12.6 (9.6) years, respectively. In addition, the TNFi group was less likely to have prior biologic use (21.7%) compared to the TOF group (67.9%). The proportion of patients in CDAI low disease activity (LDA)/remission (REM) at 6 months was 36.7% and 33.2% in the TNFi and TOF groups, respectively. The generalized linear mixed models adjusting for PS quantile showed that there was no significant difference in CDAI LDA/REM (odds ratio [OR] 0.85, 95% CI 0.51–1.43) and RADAI coefficient (OR 0.48, 95% CI –0.18 to 1.14) between the 2 groups (ref: TOF).

Conclusion. In patients with RA, physician- and patient-reported effectiveness are similar in the TNFi and TOF groups 6 months after treatment.

Key Indexing Terms: disease activity, patient-reported outcomes, rheumatoid arthritis, TNFi, treatment, tofacitinib

Rheumatoid arthritis (RA) is an immune-mediated systemic inflammatory disease typically affecting the synovial membrane and often has extraarticular manifestations.^{1,2} Tofacitinib (TOF) is an oral, small-molecule drug used to treat RA and is often chosen as an alternative to biologic disease-modifying antirheumatic drugs (bDMARDs) such as tumor necrosis factor inhibitors (TNFi). TOF is usually prescribed (5 mg twice/day) as

monotherapy or in combination with conventional synthetic (cs-) DMARDs, mostly methotrexate (MTX). The efficacy and safety of TOF have been investigated in randomized controlled trials.^{3,4,5,6,7} However, since its approval as the first Janus kinase inhibitor (JAKi), the durability and effectiveness of TOF using real-world data has been an area of interest, particularly in comparison with bDMARDs.^{8,9,10,11}

Ontario Best Practices Research Initiative (OBRI) was funded by peer-reviewed grants from the Canadian Institute for Health Research, Ontario Ministry of Health and Long-Term Care, Canadian Arthritis Network, and unrestricted grants from AbbVie, Amgen, Aurora, BMS, Celgene, Gilead, Hospira, Janssen, Lilly, Medexus, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi, and UCB. CB held a Canada Research Chair in Knowledge Transfer for Musculoskeletal Care and a Pfizer Research Chair in Rheumatology.

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ECK has received sources of funding for research from Amgen, Merck, and Pfizer; has a consulting agreement/is a member of an advisory board for AbbVie, Amgen, Celltrion, Myriad Autoimmune, F. Hoffmann-La Roche, Janssen, Lilly, Merck, Pfizer, Sandoz, Sanofi Genzyme, and Samsung Bioepis; and received speaker honoraria agreements for Amgen, AbbVie, Celltrion, F. Hoffmann-La Roche, Janssen, Merck, Pfizer, Sandoz, and Sanofi Genzyme. CB has received sources of funding for research for a longitudinal cohort study (OBRI) including psoriatic arthritis cohort (PsA) from AbbVie, Amgen, Celgene, Gilead, GSK, Janssen, Lilly, Merck, Medexus, Medreleaf/Aurora, Novartis, Pfizer (Hospira), Roche, Sandoz, Sanofi Genzyme, and UCB. The remaining authors declare no conflicts of interest relevant to this article.

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Accepted for publication January 25, 2022.

The aim of this study was to compare physician- and patient-reported outcomes (PROs) in patients treated with TNFi vs TOF, using real-world data from the Ontario Best Practices Research Initiative (OBRI). To the best of our knowledge, this study is one of the first real-world studies to thoroughly compare patient-reported effectiveness outcomes in TNFi and TOF in patients with RA, including those with prior exposure to biologic therapy.

METHODS

Data source. The OBRI is a multicenter registry that collects data from rheumatologists and patients with RA at enrollment and follow-up across Ontario, Canada. It incorporates the assessments of approximately one-third of the rheumatologists in the province of Ontario. Patients are eligible to be enrolled if they are aged ≥ 16 years at the time of diagnosis, aged ≥ 18 years at enrollment, have a rheumatologist-confirmed RA diagnosis, and have ≥ 1 swollen joint. Enrolled patients are interviewed every 6 months by phone and seen by their rheumatologist as per routine care.

Data collection. At enrollment, patients are asked for their general medical history, including comorbidity status. Rheumatologists report any history of previous comorbidities, including cardiovascular disease (CVD), RA disease activity, inflammatory markers, and tender and swollen joint counts. In addition, sociodemographic data, smoking status, height, and weight, as well as any prior and current medications, are recorded during the rheumatologist enrollment visit or the patient interview. PROs including Health Assessment Questionnaire–Disability Index (HAQ-DI), patient global assessment (PtGA), and RA Disease Activity Index (RADAI) are also collected. At follow-up visits, all the above information is updated. RA medication changes (including discontinuation and reasons for such) between visits are also captured. Rheumatologists report any comorbidities and reassess disease activity during every follow-up visit.

For this study, we selected patients with RA enrolled in the OBRI and initiating their TOF or TNFi (a list of individual TNFi has been provided in Supplementary Table 1, available from the authors on request) between

June 1, 2014 (TOF approval date in Canada) and December 31, 2019. Patients were required to have physician- and patient-reported effectiveness data available at treatment initiation and 6-month (± 2 months) follow-up. We excluded patients with low disease activity (LDA; defined as Clinical Disease Activity Index [CDAI] ≤ 10) at treatment initiation (Figure 1).

Physician-reported effectiveness outcomes. CDAI LDA/remission (REM) was defined as CDAI ≤ 10 and CDAI REM as CDAI ≤ 2.8. Disease Activity Score in 28 joints (DAS28) LDA/REM was defined as DAS28 based on erythrocyte sedimentation rate (DAS28-ESR) ≤ 3.2 and DAS28 REM as DAS28-ESR ≤ 2.6.

Patient-reported effectiveness outcomes. RADAI and its components (global pain, current disease activity, past disease activity, painful joint counts, morning stiffness), PtGA, HAQ-DI, global assessment of sleep problems, and anxiety/depression scores from the European Quality of Life (EuroQoL) questionnaire were used as patient-reported effectiveness outcomes.

Statistical analysis. All analyses were conducted on the primary analysis population. Descriptive statistics—specifically mean and SD for continuous variables—as well as counts and proportions for categorical variables were generated for all baseline characteristics. Comparisons between patients on TNFi vs TOF were conducted using the independent samples *t* test for continuous variables, and chi-square or Fisher exact tests for categorical variables.

Multiple imputation by chained equations was used to deal with missing data for covariates at treatment initiation. This model is commonly used under the assumption of missing at random. Twenty datasets were imputed and results were combined using Rubin rules.^{12,13} For 39% of patients, complete data for variables of interest were available. For 34% of patients, there were missing data for anticitrullinated protein antibody (ACPA) and complete data for the rest of the variables of interest. Data were missing for < 5% for various combinations of variables of interest. All statistical analyses were conducted using SAS 9.4 (SAS Institute).

Estimating the propensity score. We estimated propensity scores (PS) for covariates with an absolute standard difference > 0.1 between the 2 treatment groups to deal with confounding by indication. All variables except

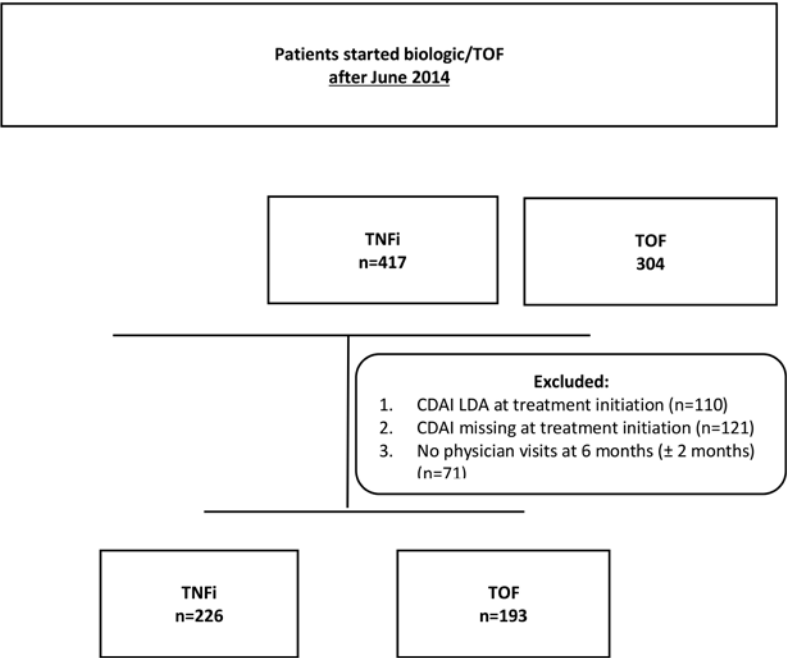


Figure 1. Study flow chart. CDAI: Clinical Disease Activity Index; LDA: low disease activity; TNFi: tumor necrosis factor inhibitor; TOF: tofacitinib.

gender, education, and rheumatoid factor (RF) were assessed at each visit. A window of 60 days was applied to capture the patient's earliest or most recent disease activity assessment at treatment initiation. For smoking status, health insurance coverage and comorbidity profile the time window was 1 year.

PS implementation and effectiveness. We compared response in patients using TNFi vs TOF with generalized linear mixed models (GLMM) with a random effect. Results are presented as odds ratios (ORs) and 95% CIs for dichotomous outcomes and coefficient and 95% CIs for continuous outcomes. In addition, we estimated the treatment effect using a PS stratification (quantiles) approach, which has been shown to remove up to 90% of the bias in the unadjusted estimate.¹⁴

We also conducted the analysis using PS weighting, including the stabilized inverse probability of treatment weight (SIPTW). Stabilized weights were used to reduce variance of the estimated treatment effect.¹⁵ The estimated weights were incorporated into a GLMM that included only the treatment variables.

We combined multiple imputations with PS using a Within approach, wherein PS individually used to obtain treatment effect estimates in each imputation were combined to produce an overall estimate.¹⁶

Ethics and consent. All sites received ethics approval to enroll patients (University Health Network REB# 07-0729 AE), and all patients provided informed consent.

RESULTS

Patient sociodemographic and clinical characteristics. Key differences in patient sociodemographics, disease activity, and medication based on type of therapy (TNFi vs TOF) are summarized in Table 1. Patients treated with TNFi were significantly younger compared to those treated with TOF (mean 56.5 vs 60.3 yrs). Patients in the TOF group were more likely to have health insurance coverage compared to patients in the TNFi group (85.1% vs 77.8%). No significant difference in sex was observed between groups.

Patients treated with TOF were more likely to have longer mean disease duration (12.6 vs 8.0 years; $P < 0.001$), less likely to be bDMARD-naïve (32.1% vs 78.3%, $P < 0.001$), less likely to use hydroxychloroquine (HCQ; 23.3% vs 37.6%; $P = 0.002$), less likely to use conventional synthetic DMARDs (csDMARDs; 73.6% vs 81.0%), and more likely to use concomitant steroids (26.4% vs 15.5%; $P = 0.006$), compared to those treated with TNFi (Table 1). Further, at baseline, patients taking TOF reported significantly worse physical function as indicated by the higher mean HAQ-DI (1.4 vs 1.2; $P = 0.02$), more sleep problems (4.8 vs 4.1; $P = 0.05$), and higher prevalence of CVD (11.4% vs 5.8%, $P = 0.03$; Table 1).

Absolute standardized difference between the 2 treatment groups at baseline was $> 10\%$ for age, health insurance coverage, RA duration, positive RF, positive ACPA, C-reactive protein, HAQ-DI, sleep problems, anxiety/depression score, CVD, hypertension, first use of treatment, number of prior biologics used, concomitant HCQ, concomitant csDMARD, and concomitant steroid use. Thus, these covariates were used to calculate PS (Table 1). To avoid collinearity between individual csDMARDs, we did not use concomitant use of csDMARDs overall for the calculation of PS.

Physician-reported effectiveness outcomes. The proportion of patients in CDAI LDA/REM at 6 months was 36.7% and

33.2% in the TNFi and TOF groups, respectively. CDAI remission was reported in 24 patients (10.6%) in the TNFi group and 13 (6.7%) in the TOF group. DAS28-ESR LDA/REM was reported in 92 (40.7%) and 69 (35.8%) in the TNFi and TOF groups, respectively. However, DAS28-ESR REM in the TNFi group (29.2%) was significantly higher compared to the TOF group (20.2%; Table 2). No significant difference was found for change in CDAI and DAS28-ESR between the 2 treatment groups.

In the univariable analysis, patients initiating TNFi therapy had higher numerical responses as shown by CDAI and DAS28-ESR scores, compared to patients initiating TOF therapy (Supplementary Table 1, available from the authors on request). Adjusting for stratification (quantiles) and SIPTW across 20 multiple imputed datasets resulted in reduced and nonsignificant ORs compared to the unadjusted estimates. For example, as shown in Table 3, there was no significant difference for CDAI LDA/REM between the 2 treatment groups after adjusting for PS quantile (OR 0.85, 95% CI 0.51–1.43) or SIPTW (OR 0.93; 95% CI 0.59–1.49). The results were consistent for other physician-assessed measures of disease activity (DAS28-ESR).

Patient-reported effectiveness outcomes. In terms of PROs, we found no significant difference in the mean change at 6 months between the 2 treatment groups. The mean change at 6 months for HAQ-DI was -0.10 and -0.06 in the TNFi and TOF groups, respectively ($P > 0.05$). We also found no significant difference in the mean change in RADAI (TNFi -0.75 vs TOF -0.63) and its components between the 2 treatment groups (Table 2).

In the unadjusted GLMM model, HAQ-DI (coefficient: -0.20 , 95% CI -0.34 to -0.06), PtGA (-0.42 , 95% CI -0.84 to -0.01), and sleep problems (-0.58 , 95% CI -1.15 to -0.01) showed significantly less improvement in the TNFi group compared to the TOF group (Supplementary Table 2, available from the authors on request). Upon adjustment for stratification (quantiles) and SIPTW, there was no significant difference between the 2 groups for these variables. Other PROs, including RADAI, were not significantly different between the 2 treatment groups (Table 4).

DISCUSSION

This real-world observational study directly compares response in patients with RA initiating TNFi vs TOF. We found that patients initiating TOF had a longer disease duration (12.6 vs 8.0 years, $P < 0.001$) and were more likely to have prior biologic use (78.3% vs 32.1%, $P < 0.001$) than those initiating a TNFi. Similar results were reported by Reed et al in 2019 using the US Corrona registry data.¹⁰ We also showed that TOF is more commonly used as monotherapy compared to TNFi (concomitant csDMARDs: 73.6% vs 81.0%), a result reported by other studies.^{10,17}

In the present study, CDAI LDA/REM at 6 months for TNFi and TOF was 36.7% and 33.2%, respectively, with a nonsignificant difference. Similar to our findings, Reed et al in 2019 also found no significant difference for CDAI LDA/REM

Table 1. Patient baseline characteristics overall and by treatment.

	Treatment			Absolute Standardized Difference
	Total, n = 419	TNFi, n = 226	TOF, n =193	
Sociodemographics				
Gender, female, n (%)	349 (83.3)	185 (81.9)	164 (85.0)	0.08
Age, yrs, mean ± SD ^a	58.3 ± 12.6	56.5 ± 13.4	60.3 ± 11.2	0.30
Health insurance coverage ^a , n	386	212	174	
Public (OHIP) + private or ODB, n (%)	313 (81.1)	165 (77.8)	148 (85.1)	0.19
Disease activity				
Disease duration at treatment initiation ^a , n	417	226	191	
Yrs, mean ± SD	10.1 ± 9.4	8.0 ± 8.7	12.6 ± 9.6	0.50
RF positive ^a , n	386	211	175	
n (%)	276 (71.5)	156 (73.9)	120 (68.6)	0.12
ACPA positive ^a , n	216	129	87	
n (%)	131 (60.6)	86 (66.7)	45 (51.7)	0.31
CRP ^a , n	408	219	189	
mg/L, mean ± SD	11.7 ± 19.0	12.8 ± 18.6	10.5 ± 19.3	0.12
CDAI (0–76), n	419	226	193	
Mean ± SD	26.6 ± 10.5	26.3 ± 10.1	27.0 ± 11.0	0.07
PROs				
HAQ-DI (0–3) ^a , n	374	197	177	
Mean ± SD	1.3 ± 0.8	1.2 ± 0.8	1.4 ± 0.7	0.24
RADAI (0–10), n	374	197	177	
Mean ± SD	3.9 ± 3.4	3.9 ± 3.4	3.8 ± 3.4	0.03
Sleep problems (0–10) ^a , n	374	197	177	
Mean ± SD	4.4 ± 3.4	4.1 ± 3.4	4.8 ± 3.4	0.28
Depression and anxiety score (0–10) ^a , n	374	197	177	
Mean ± SD	2.5 ± 2.0	2.4 ± 2.0	2.6 ± 2.1	2.8
Comorbidities				
CVD ^a , n	416	224	192	
n (%)	35 (8.4)	13 (5.8)	22 (11.4)	0.20
Hypertension ^a , n	417	225	192	
n (%)	119 (28.5)	58 (25.8)	61 (31.8)	0.13
Medication				
First use ^a , n (%)	239 (57.0)	177 (78.3)	62 (32.1)	1.5
No. of prior biologics ^a , mean ± SD	0.8 ± 1.3	0.3 ± 0.7	1.4 ± 1.5	0.99
Concomitant medication				
MTX, n (%)	214 (51.1)	117 (51.8)	97 (50.3)	0.03
HCQ ^a , n (%)	130 (31.0)	85 (37.6)	45 (23.3)	0.31
csDMARDs, n (%)	325 (77.6)	183 (81.0)	142 (73.6)	0.17
Steroids ^a , n (%)	86 (20.5)	35 (15.5)	51 (26.4)	0.27

No. of available data (n) is presented when the complete data were not available. Values in bold are statistically significant ($P < 0.05$). ^a Variables with an absolute standard difference $> 10\%$ between TOF and TNFi treatment group at baseline; these variables (except csDMARDs) were used to calculate the propensity score. ACPA: anticitrullinated protein antibody; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CVD: cardiovascular disease; HAQ-DI: Health Assessment Questionnaire–Disability Index; HCQ: hydroxychloroquine; MTX: methotrexate; ODB: Ontario Drug Benefit; OHIP: Ontario Health Insurance Plan; PRO: patient-reported outcome; RADAI: Rheumatoid Arthritis Disease Activity Index; RF: rheumatoid factor; TNFi: tumor necrosis factor inhibitor; TOF: tofacitinib.

between TNFi (38.7%) and TOF (36.0%) combination therapy at 6 months' follow-up.¹⁰

The results of our study suggest that, after adjusting for differences in baseline characteristics that may have contributed to which treatment patients received, patients with RA initiated on TNFi agents had a similar response to those initiated on TOF, a targeted synthetic DMARD.

In this analysis, we focused on patient-reported effectiveness outcomes and found no significant difference between the

2 treatment arms. For example, the mean change (SD) for pain was -0.92 (2.75) and -0.74 (2.46) for TNFi and TOF, respectively. Several randomized controlled trials have included PROs as part of efficacy measures for investigating TOF or TNFi treatment.^{18–31} However, fewer real-world studies have compared PROs between these 2 treatment arms. Reed et al showed that the mean pain (visual analog scale) score for TNFi and TOF users was not significantly different (42.7 and 46.9, respectively) at 6 months' follow-up.

Table 2. Effectiveness and functional improvement at 6-month follow-up by treatment group (n = 419).

	Treatment		
	TNFi, n = 226	TOF, n = 193	<i>P</i>
Physician assessment			
CDAI			
LDA/REM, n (%)	83 (36.7)	64 (33.2)	0.45
REM, n (%)	24 (10.6)	13 (6.7)	0.16
Change	-10.5 (12.7)	-10.1 (14.0)	0.76
DAS28-ESR			
LDA/REM, n (%)	92 (40.7)	69 (35.8)	0.30
REM, n (%)	66 (29.2)	39 (20.2)	0.03
Change	-1.18 (1.5)	-0.96 (1.5)	0.16
PROs, mean change from baseline			
HAQ-DI	-0.10 (0.52)	-0.06 (0.61)	0.45
PtGA	-1.43 (2.88)	-1.44 (2.94)	0.97
Fatigue	-0.49 (3.06)	-0.44 (2.81)	0.86
RADAI	-0.75 (3.47)	-0.63 (3.17)	0.71
Global pain	-0.92 (2.75)	-0.74 (2.46)	0.51
Current disease activity	-0.91 (3.06)	-0.88 (3.01)	0.92
Past disease activity	-0.67 (2.68)	-0.54 (2.42)	0.62
Painful joint count	1.17 (2.00)	1.20 (2.11)	0.90
Morning stiffness	-1.25 (3.42)	-1.07 (3.48)	0.63
Sleep problems	-0.62 (3.43)	-0.73 (3.21)	0.73
Depression	-0.43 (2.09)	-0.54 (1.96)	0.57

Values are expressed as mean (SD) unless otherwise indicated. CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire–Disability Index; LDA: low disease activity; PRO: patient-reported outcome; PtGA: patient global assessment; RADAI: Rheumatoid Arthritis Disease Activity Index; REM: remission; TNFi: tumor necrosis factor inhibitor; TOF: tofacitinib.

The strengths of our study include the use of multicenter data, and controlling for disease severity, comorbidities, and demographics to balance measurable potential confounders by adjusting our models for a PS. In observational studies, treatment effects are assessed by comparing the exposed and nonexposed groups. The exposed group may be different from the nonexposed group with respect to factors (eg, disease severity) other than treatment. Thus, direct comparisons of the 2 groups may be misleading and result in biased estimates of the treatment effect. The PS is a balancing score that can be used to compare 2 groups and obtain an unbiased estimate.¹⁴

There are some limitations to this study. Given the lack of randomization and despite the use of PS adjustment, our estimates may still be biased due to some unmeasured or residual confounders that may be related to the study design or registry data collection methods. Additionally, there are likely systematic differences in the practice patterns of physicians participating in the OBRI.

In summary, physician- and patient-reported effectiveness outcomes in patients with RA were similar in the TNFi and TOF groups 6 months after treatment. In addition, there was a positive association between physician-reported effectiveness and improvement in PROs.

Table 3. Effect of treatment on clinical disease activity using general linear mixed models adjusted for propensity score (PS) on multiple imputed data.

	TNFi vs TOF	
	PS Stratification (PS Quantile), n = 419 OR (95% CI), P	SIPTW, n = 368 OR (95% CI), P
CDAI LDA/REM	0.85 (0.51–1.43), 0.55	0.93 (0.59–1.49), 0.78
CDAI REM	1.29 (0.24–6.84), 0.76	1.26 (0.28–5.59), 0.76
DAS28-ESR LDA/ REM	0.66 (0.36–1.20), 0.17	0.83 (0.49–1.40), 0.49
DAS28-ESR REM	0.87 (0.41–1.89), 0.72	1.10 (0.57–2.15), 0.78

PS was estimated for covariates with lack of balance between TNFi and TOF (absolute standard difference > 10%) at treatment initiation (age, health insurance coverage, RA duration, hypertension, cardiovascular disease, anxiety/depression score, sleep problem, RF, ACPA, CRP, HAQ-DI, first use of treatment, no. of prior biologics used, and concomitant HCQ and steroid use). Multiple imputed data was applied using fully conditional specification (multiple imputations by chained equations). ACPA: anticitrullinated protein antibody; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; LDA: low disease activity; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; HAQ-DI: Health Assessment Questionnaire–Disability Index; CRP: C-reactive protein; HCQ: hydroxychloroquine; OR: odds ratio; RA: rheumatoid arthritis; REM: remission; RF: rheumatoid factor; SIPTW: stabilized inverse probability treatment weight; TNFi: tumor necrosis factor inhibitor; TOF: tofacitinib.

Table 4. Effect of treatment on PROs using general linear mixed models unadjusted and adjusted for propensity score (PS) on multiple imputed data.

	TNFi vs TOF	
	PS Stratification (PS Quantile), n = 419 Coefficient (95% CI), P	SIPTW, n = 368 Coefficient (95% CI), P
HAQ-DI	-0.01 (-0.18, 0.16), 0.88	-0.01 (-0.25, 0.05), 0.19
PtGA	0.003 (-0.49, 0.50), 0.99	-0.11 (-0.57, 0.34), 0.63
Fatigue	0.41 (-0.20, 1.03), 0.19	0.19 (-0.37, 0.76), 0.50
RADAI	0.48 (-0.18, 1.14), 0.16	0.35 (-0.23, 0.93), 0.24
Global pain	0.10 (-0.48, 0.68), 0.74	-0.09 (-0.60, 0.42), 0.73
Current disease activity	0.03 (-0.56, 0.61), 0.93	-0.06 (-0.59, 0.46), 0.81
Past disease activity	0.02 (-0.48, 0.51), 0.95	0.06 (-0.34, 0.47), 0.75
Painful joint count	0.15 (-0.31, 0.62), 0.52	0.06 (-0.34, 0.45), 0.75
Morning stiffness	-0.01 (-0.11, 0.09), 0.89	-0.03 (-0.12, 0.06), 0.54
Sleep problem	-0.25 (-0.95, 0.45), 0.49	-0.21 (-0.82, 0.40), 0.50
Depression score	0.12 (-0.35, 0.58), 0.62	0.09 (-0.31, 0.49), 0.57

PS was estimated for covariates with lack of balance between TNFi and TOF (absolute standard difference > 10%) at treatment initiation (age, health insurance coverage, RA duration, hypertension, cardiovascular disease, anxiety/depression score, sleep problem, RF, ACPA, CRP, HAQ-DI, first use of treatment, no. of prior biologics used, and concomitant HCQ and steroid use). Multiple imputed data was applied using fully conditional specification (multiple imputations by chained equations; n = 20). ACPA: anticitrullinated protein antibody; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire–Disability Index; HCQ: hydroxychloroquine; PS: propensity score; PtGA: patient global assessment; RA: rheumatoid arthritis; RADAI: RA Disease Activity Index; RF: rheumatoid factor; SIPTW: stabilized inverse probability treatment weight; TNFi: tumor necrosis factor inhibitor; TOF: tofacitinib.

ACKNOWLEDGMENT

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

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