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Tofacitinib Persistence in Patients with Rheumatoid Arthritis: A Retrospective Cohort Study

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ABSTRACT. ***Objective.*** To compare medication persistence of tofacitinib with persistence of injectable biological disease-modifying antirheumatic drugs (bDMARD) in patients with rheumatoid arthritis (RA).

Methods. We performed a retrospective new-user cohort study of patients with RA in the IBM MarketScan Research Databases. New users of tofacitinib or bDMARD were identified between November 2012 and December 2016. Persistence, in number of years, was the time between treatment initiation and the earliest occurrence of discontinuation or switching from the medication prescribed at cohort entry. Persistence of tofacitinib was compared with bDMARD persistence using Cox proportional hazards regression with adjustment for high-dimensional propensity scores. Similar methods were used for an analysis of post first-line therapy in patients who switched to tofacitinib from a bDMARD.

Results. New tofacitinib users (n = 1031) were 56 years of age, on average, and 82% were women. New bDMARD users (n = 17,803) were 53 years of age, on average, and 78% were women. New tofacitinib users had shorter medication persistence (median 0.81 yrs) compared to bDMARD patients (1.02 yrs). After adjustment, the HR for discontinuation of tofacitinib compared with bDMARD was 1.14 (95% CI 1.05–1.25). Patients who switched to tofacitinib from a bDMARD had longer persistence than patients who switched to a bDMARD (adjusted HR for discontinuation 0.90, 95% CI 0.83–0.97).

Conclusion. Further research is warranted to understand the reasons for discontinuation of tofacitinib despite its ease of administration and to understand the observed differences between switchers and new users.

Key Indexing Terms: biological therapy, Janus kinase inhibitors, medication adherence, rheumatoid arthritis

Tofacitinib is a Janus kinase inhibitor indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adults who demonstrate inadequate response or intolerance to methotrexate (MTX)[1]. Tofacitinib, a small molecule administered orally, may provide a convenience advantage over the injectable biological disease-modifying antirheumatic drugs (bDMARD). Approved by the US Food and Drug Administration in November 2012[2], tofacitinib is a relatively new medication, and evidence of its effectiveness and safety is based mainly on randomized controlled trials (RCT). The efficacy and safety of tofacitinib were shown to be comparable with, or noninferior to, bDMARD in RCT of 6–24 months[3,4,5,6] and in network metaanalyses[7,8]. Additionally, long-term extensions of RCT showed that efficacy, in terms of the American College of Rheumatology 20/50/70 criteria (ACR20/50/70), was maintained[9]. Approximately one-quarter of patients discontinued treatment due to adverse events after 8 years[9]. However, RCT participants may not represent patients treated in the real-world setting[10,11], and RCT are usually short compared to lifelong treatment of a chronic disease.

Medication persistence is a measure of adherence[12] and has been proposed as a surrogate measure for medication effectiveness[13]. Nevertheless, persistence is affected by other factors, such as out-of-pocket costs[14,15] and prescriber preference[16]. Based on the evidence that RA patients prefer oral medications over subcutaneous and intravenous medications[17], and that efficacy reported in RCT is similar for tofacitinib and bDMARD[4,5,6,7,8], it is reasonable to expect that patients taking tofacitinib would adhere to treatment longer than patients taking bDMARD. However, mounting evidence shows that adherence during the implementation phase is often worse with tofacitinib[18,19,20].

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The opinions, results, and conclusions reported in this paper are those of the authors. No endorsement by the data holder is intended, nor should it be inferred.

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Notably, one study of switchers that compared tofacitinib and bDMARD persistence found similar mean persistence in the first year after switching[21]. To the best of our knowledge, no published study of new users has compared persistence of tofacitinib with persistence of bDMARD.

The main objective of our study was to compare medication persistence in new users of tofacitinib with new users of bDMARD. A secondary objective was to compare persistence in patients who switched from a bDMARD to tofacitinib with those who switched from tofacitinib or a bDMARD to another bDMARD.

MATERIALS AND METHODS

Cohorts of RA patients. This study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES)[22]. The study protocol was approved by the University of British Columbia Clinical Research Ethics Board (number H16-00137). We conducted a cohort study using the IBM MarketScan Research Databases (Commercial and Medicare, 2010–2016). The source population consisted of more than 70 million individuals aged 18 years and older who had medical services coverage between November 2012 and December 2015. We selected medical and pharmacy records of new prescriptions for tofacitinib and the following bDMARD: adalimumab (ADA), certolizumab pegol (CZP), etanercept (ETN), golimumab (GOL), infliximab (IFX), abatacept (ABA), and tocilizumab (TCZ). New users, sometimes referred to as biologic-naïve users, were individuals who had no prescriptions (in pharmacy or medical records) for any of the above medications, or for anakinra or rituximab (RTX) in the previous year. RTX was not included in our analysis due to the uncharacteristically long interval between injections (median time between doses of 7–8 months)[23]. New users of anakinra were excluded posthoc when we discovered that they were markedly older and had more comorbidities than patients who started using other bDMARD.

Patients were required to be enrolled in their health plan for at least 1 year prior to receiving a prescription for tofacitinib or a bDMARD. Short gaps in medical coverage up to 90 days were permitted. Patients were identified as having RA if, in the 2 years before receiving their new prescription for tofacitinib or a bDMARD, they had a discharge abstract from an acute care hospital or an outpatient medical record which included an International Classification of Diseases, 9th revision (ICD-9) code of 714.XX or an ICD-10 code of M05.XX. A previous validation study estimated a sensitivity of 93% and a specificity of 84% for an RA diagnosis based on 1 physician visit and at least 1 prescription for a conventional disease-modifying antirheumatic drug or bDMARD[24]. We excluded patients who received a different medication (tofacitinib or bDMARD) within 1 week of cohort entry, or who were 21 years of age or younger (to eliminate cases of juvenile idiopathic arthritis). Patients were also excluded if they had been diagnosed with malignancy, juvenile chronic polyarthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, regional enteritis, or ulcerative colitis in the 2 years before cohort entry. Patients entered the study once on the earliest date of receiving a new prescription.

For our secondary objective, we constructed a cohort of patients with RA who switched from a bDMARD to tofacitinib, and patients who switched from 1 bDMARD to another bDMARD or from tofacitinib to a bDMARD. Switchers, sometimes referred to as biologic-experienced users, were patients who had used different medications (tofacitinib or any bDMARD) in the previous year but were new users of the medication prescribed at cohort entry (i.e., the target medication). We applied the same inclusion and exclusion criteria as for the primary objective.

Outcome measures. Persistence was measured in number of years from cohort entry until discontinuation of the medication, which was defined as stopping the target medication or switching to another medication. Discontinuation was ascertained from pharmacy and medical prescription records using a refill-sequence model[25] and was defined as the first medication-free gap exceeding 90 days from the expected prescription refill date for the target medication. The date of discontinuation was defined as the date the refill was expected to occur. To estimate the expected refill date, we used the recorded days of medication supplied, which usually reflected the number of consecutive days until the next prescription refill. When days' supply of an injectable medication was missing or invalid, it was imputed as the longest dosing interval recommended in the product monograph. Days' supply was truncated at 180 days and no stockpiling was allowed. Patients who received prescriptions for different medications (tofacitinib, bDMARD, RTX, or anakinra) before they had discontinued using their target medication were considered switchers, and the discontinuation date was defined as the date when the new medication was dispensed or administered. Patients were censored at the end of their health plan enrollment, when they experienced an enrollment gap longer than 90 days, or at the end of the study period (December 31, 2016). Data on death were unavailable in the MarketScan Research Databases; therefore, we were unable to account for death as a competing risk.

Statistical analysis. The risk of discontinuing tofacitinib was compared with that of bDMARD using Cox proportional hazards regression (i.e., outcome models). We estimated high-dimensional propensity scores (hdPS)[26], which was the probability of an individual being treated with tofacitinib compared to bDMARD. The hdPS models included demographics and clinical variables that were forced into the model and a large number of covariates identified from drug dispensations, and inpatient and outpatient diagnoses and medical procedures from the year before cohort entry. Demographic factors at cohort entry included sex, age, income (based on Metropolitan Statistical Areas), and information on employment, health plan, and geographical area. Clinical variables measured in the year before cohort entry included the use of any prescription nonsteroidal antiinflammatory drug, the Deyo-Charlson comorbidity score[27], days with ambulatory visits to a physician's office, and days in hospital. We excluded patients in the nonoverlapping tails of the distributions[28] and then calculated the hdPS deciles.

The adjusted outcome models included hdPS deciles and 2 categorical adherence variables to partially compensate for any potential channeling bias. Channeling bias may occur when the newly marketed tofacitinib and established bDMARD, despite similar indications, are prescribed to patients with different prognostic characteristics. We considered that the patients' medication adherence behavior may have affected the decision to choose tofacitinib versus bDMARD. We assessed historical adherence rates for oral or injectable medications separately from dispensations of oral or injectable antirheumatic medications and oral antihypertensive and anti-diabetic medications in the 2 years before cohort entry[29] (Supplementary Table 1, available with the online version of this article). We calculated the medication possession ratio (MPR) of each medication used and averaged the MPR separately for oral and injectable medications. The average values were the historical adherence rates. Each of the 2 historical adherence variables had 3 levels: "adherent" when the mean historical adherence rate was 0.8 or higher; "nonadherent"; and "unavailable" for patients not treated with these medications or who received only a single prescription for each medication. Details of the method used to assign the 3-level adherence variables are included in the Supplementary Data 1 (available with the online version of this article).

Additional analyses. We analyzed cohorts of patients who had received at least 2 prescriptions of the target medication in order to reduce the risk of selection bias caused by including patients who refilled their prescription but did not initiate the medication after the refill. Further, we assessed the robustness of the 90-day medication-free gap that was used to identify discontinuation by reanalyzing the data using gaps of 60 and 180 days. We also analyzed subcohorts of patients who did not receive concomitant MTX treatment in order to examine whether tofacitinib had a persistence advantage in those patients. Concomitant MTX treatment was defined as at least 1 MTX dispensation in the 6 months before cohort entry. Finally, we

explored possible effect modification by historical medication adherence by separately analyzing subgroups of patients based on their adherence levels.

RESULTS

The cohort of new users consisted of 1031 tofacitinib and 17,803 bDMARD patients (Table 1; Supplementary Figure 1, and Supplementary Table 2, available with the online version of this article). New tofacitinib patients were 56 years of age, on average, and 82% were women. New bDMARD patients were 53 years of age, on average, and 78% were women. Patients treated with tofacitinib had more comorbidities and were more adherent to earlier treatments for RA, hypertension, and diabetes, either oral or injectable. Tofacitinib patients also used less MTX but more leflunomide and prednisone. By the end of follow-up, 9929 individuals had not persisted with their medication, including 591 (57.3%) tofacitinib users and 9338 (52.5%) bDMARD users. New users of tofacitinib had shorter persistence than new users of bDMARD (Figure 1A, Table 2). Median persistence was 0.81 years for tofacitinib users (95% CI 0.73–0.91) and 1.02 years for bDMARD users (95% CI 0.99–1.05). The crude and adjusted HR for discontinuation of tofacitinib compared with bDMARD were 1.18 (95% CI 1.09–1.28) and 1.14 (95% CI 1.05–1.25), respectively.

We observed heterogeneity in comparisons of tofacitinib and the individual bDMARD (Table 2; Supplementary Figure 2, available with the online version of this article). Tofacitinib was associated with a greater, albeit heterogeneous, hazard of medication discontinuation compared with ADA, ETN, GOL, and IFX (range: HR 1.13–1.37). No difference in the comparisons of ABA and TCZ was observed.

In our analysis of switchers, we identified 1535 RA patients who switched to tofacitinib from a bDMARD, and 9849 patients who switched from 1 bDMARD to another or from tofacitinib to a bDMARD (Table 1; Supplementary Figure 1 and Supplementary Table 3, available with the online version of this article). Switchers to tofacitinib were 54 years of age, on average, and 83% were women. Switchers to bDMARD were 53 years of age, on average, and 81% were women. In contrast to new users, switchers to tofacitinib had longer persistence than switchers to bDMARD (Figure 1B, Table 3, Supplementary Figure 3). Median persistence was 1.04 years in switchers to tofacitinib (95% CI 0.94–1.19) and 0.83 years in switchers to bDMARD (95% CI 0.78–0.86). The adjusted HR of medication discontinuation after switching to tofacitinib compared with switching to bDMARD was 0.90 (95% CI 0.83–0.97).

Results of additional analyses. Kaplan-Meier plots indicated a sizable decrease in medication persistence within 1 month of initiation (Figure 1). Considering that 83% of the first dispensations of tofacitinib were for 30 days, the sizable decrease in medication persistence was likely due to patients who discontinued treatment after a single prescription and those who refilled prescriptions but did not initiate the medication following the refill. The decrease in persistence was larger in tofacitinib patients in both cohorts (new users and switchers). Among new users, 21.9% of tofacitinib patients did not refill a second prescription compared with 13.9% of bDMARD users; only about 3% in each group were censored after the first dose. Among switchers, the proportions were 17.7% and 12.6%, respectively; with similar percentages (3%) of patients censored after the first dose. The exclusion of patients who received a single prescription of the target medication did not affect the significance of the results for switchers (Table 4); the adjusted HR was 0.81 (95% CI 0.74–0.88). Among new users, excluding patients who received a single prescription of the medications had a significant effect on the estimates and the adjusted HR of 0.99 became insignificant (95% CI 0.89–1.10). These results are supported by the patterns of the Kaplan-Meier plot in Figure 1A: After the sizable decrease during the first month after cohort entry, persistence curves for tofacitinib and bDMARD users appear to be parallel. The length of the medication-free gap influenced the magnitude of the HR estimates (Table 4), but the results remained statistically significant. Finally, in new users who did not receive concomitant MTX treatment, the HR remained significant, with longer persistence for bDMARD. However, in switchers who did not receive concomitant MTX treatment, tofacitinib lost its benefit in terms of persistence, and the HR became statistically insignificant.

To explore the influence of historical adherence to treatments on persistence, we estimated HR separately for each category of the 2 historical adherence variables (Table 5). The concordance rate between the historical adherence to oral medications and the historical adherence to injectable medications was about 57% (Supplementary Table 4, available with the online version of this article). In new users, estimates of historical adherence to injectable medications did not reach the significance level, probably due to the lack of data on adherence of these medications. Historical adherence to oral medications is likely an effect modifier in new users: in adherent patients, the discontinuation rates were lower, albeit insignificant, with tofacitinib (HR 0.95, 95% CI 0.83–1.08), while in nonadherent patients, the discontinuation rates were higher with tofacitinib (HR 1.33, 95% CI 1.17–1.52). Historical adherence to oral or injectable medications had no effect in switchers, who had consistently lower discontinuation rates with tofacitinib (range: HR 0.76–0.91).

DISCUSSION

To our knowledge, this study is the largest to date that compares persistence of tofacitinib with persistence of bDMARD among patients with RA, and the only comparative study conducted with new users of these medications. In the IBM MarketScan Research Databases, new users of tofacitinib had a shorter persistence compared with new users of bDMARD. In contrast, for patients who had already used a bDMARD or tofacitinib and started a new medication, we found a significantly longer persistence for switchers to tofacitinib compared with switchers to bDMARD. In addition, we observed longer persistence in switchers to tofacitinib compared with new users of the medication. The results of both analyses were robust, and adjustment for hdPS had little influence on our HR and no effect on statistical significance. We also found that historical adherence to oral medications is likely an effect modifier in new users, and patients continue their oral adherence behavior when treated

Table 1. Patients' baseline characteristics.

	New Users of		Switchers to	
	Tofacitinib, n = 1031	bDMARD, n = 17,803	Tofacitinib, n = 1535	bDMARD, n = 9849
Duration of available follow-up[†], yrs, mean (SD)	1.70 (0.98)	1.73 (1.08)	1.74 (1.07)	1.74 (1.1)
Demographics				
Female	844 (81.9)	13,925 (78.2)	1278 (83.3)	8001 (81.2)
Age, yrs, mean (SD)	56.4 (11.3)	52.9 (12.0)	53.9 (11.1)	52.9 (11.6)
Socioeconomic status				
Low	192 (18.6)	3279 (18.4)	275 (17.9)	1844 (18.7)
2nd quarter	158 (15.3)	3196 (18.0)	313 (20.4)	1932 (19.6)
3rd quarter	197 (19.1)	3284 (18.5)	284 (18.5)	1780 (18.1)
High	188 (18.2)	3289 (18.5)	285 (18.6)	1834 (18.6)
Unknown	296 (28.7)	4755 (26.7)	378 (24.6)	2459 (25.0)
Relation to Employee				
Employee	622 (60.3)	11,245 (63.2)	859 (56.0)	6044 (61.4)
Spouse/dependent	409 (39.7)	6558 (36.8)	676 (44.0)	3805 (38.6)
Employment Status				
Active full-time/part-time	462 (44.8)	8187 (46.0)	784 (51.1)	4871 (49.5)
Retiree	240 (23.3)	2853 (16.0)	300 (19.6)	1680 (17.1)
Other/unknown	329 (31.9)	6763 (38.0)	451 (29.4)	3298 (33.5)
Region				
Northeast	206 (20.0)	2777 (15.6)	262 (17.1)	1596 (16.2)
North-central	194 (18.8)	3700 (20.8)	289 (18.8)	2019 (20.5)
South	451 (43.7)	7745 (43.5)	690 (45.0)	4143 (42.1)
West	156 (15.1)	3060 (17.2)	257 (16.7)	1891 (19.2)
Unknown	24 (2.3)	521 (2.9)	37 (2.4)	200 (2.0)
Industry				
Manufacturing	232 (22.5)	3726 (20.9)	351 (22.9)	2114 (21.5)
Transportation, communications, utilities	153 (14.8)	1929 (10.8)	191 (12.4)	1152 (11.7)
Retail trade	25 (2.4)	528 (3.0)	49 (3.2)	328 (3.3)
Finance, insurance, real estate	73 (7.1)	1324 (7.4)	132 (8.6)	744 (7.6)
Services	136 (13.2)	2865 (16.1)	264 (17.2)	1659 (16.8)
Other/unknown	412 (40.0)	7431 (41.7)	548 (35.7)	3852 (39.1)
Clinical status and comorbidities				
Deyo comorbidity score = 0	609 (59.1)	11,879 (66.7)	1012 (65.9)	6717 (68.2)
Pleural effusion	27 (2.6)	319 (1.8)	32 (2.1)	174 (1.8)
No. days with ambulatory visits, mean (SD)	21.8 (16.6)	19.9 (15.4)	23.1 (17.0)	22.6 (15.8)
No. days in hospital, mean (SD)	0.9 (3.9)	0.5 (2.6)	0.7 (2.8)	0.5 (2.7)
Use of medications in the previous year				
Azathioprine	31 (3.0)	318 (1.8)	38 (2.5)	209 (2.1)
Hydroxychloroquine	257 (24.9)	4751 (26.7)	313 (20.4)	2181 (22.1)
Leflunomide	215 (20.9)	2349 (13.2)	274 (17.9)	1633 (16.6)
Methotrexate	549 (53.2)	10,566 (59.3)	796 (51.9)	5476 (55.6)
Minocycline	16 (1.6)	205 (1.2)	32 (2.1)	108 (1.1)
Sulfasalazine	115 (11.2)	1814 (10.2)	108 (7.0)	797 (8.1)
Prednisone	651 (63.1)	9871 (55.4)	956 (62.3)	5969 (60.6)
Nonsteroidal antiinflammatory drugs	164 (15.9)	2614 (14.7)	232 (15.1)	1543 (15.7)
> 1 different bDMARD or tofacitinib	–	–	191 (12.4)	656 (6.7)
Adherent to earlier medication therapy[‡]				
Oral therapy				
Adherent	519 (50.3)	7627 (42.8)	760 (49.5)	4680 (47.5)
Nonadherent	411 (39.9)	6499 (36.5)	659 (42.9)	4115 (41.8)
Unavailable	101 (9.8)	3677 (20.7)	116 (7.6)	1054 (10.7)
Injectable therapy				
Adherent	86 (8.3)	915 (5.1)	576 (37.5)	3514 (35.7)
Nonadherent	56 (5.4)	1288 (7.2)	307 (20.0)	1804 (18.3)
Unavailable	889 (86.2)	15,600 (87.6)	652 (42.5)	4531 (46.0)

Data are presented as n (%) treated with this medication, unless otherwise specified. Diagnosis of ascites and use of aurothiomalate, cyclosporine, and penicillamine in the previous year are not shown due to the rarity of this use (i.e., there were < 25 users in each cohort). [†] Duration of available follow-up was measured from cohort entry until the end of enrollment, defined as a gap of 90 days or longer, or the end of the study period (December 31, 2016). [‡] Users were defined as adherent to earlier medication therapy if the mean medication possession ratio for oral or injectable antihypertensive, antidiabetic, and antirheumatic medication prescribed in the 2 years before cohort entry was 80% or greater. Adherence "unknown" was assigned if the patients did not obtain any of the medications or had only 1 dispensation. See the Supplementary Materials for details (available with the online version of this article). bDMARD: biological disease-modifying antirheumatic drug.

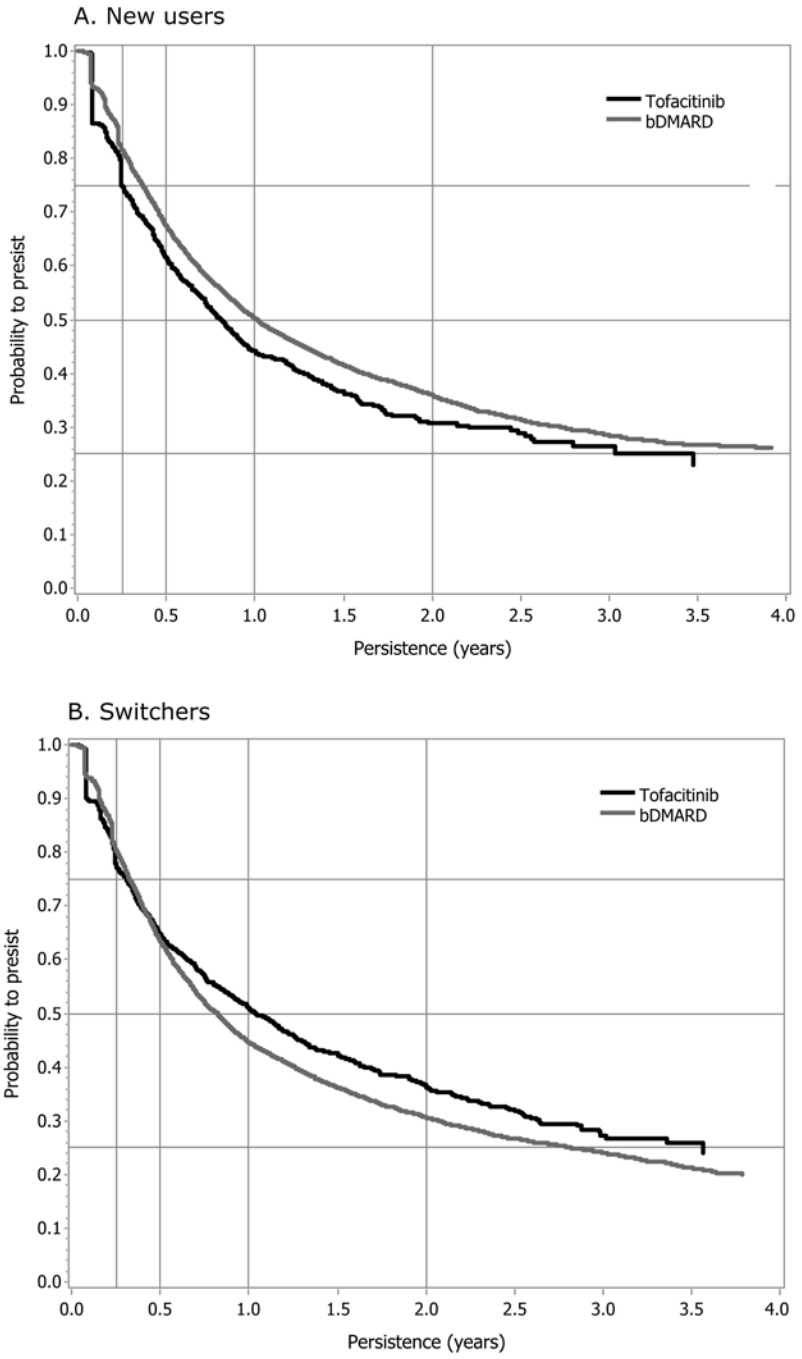

Figure 1. Kaplan-Meier estimates of medication persistence in new users and switchers. bDMARD: biological disease-modifying antirheumatic drugs.

with tofacitinib. Historical adherence had no effect in switchers.

Evidence of treatment persistence of tofacitinib is available from RCT and real-world data, including a previous metaanalysis that pooled the discontinuation rates of tofacitinib and bDMARD from RCT[30]. Similar to our study, the metaanalysis indicated that new users of ABA had lower discontinuation rates than new users of tofacitinib. Unlike our analyses, discontinuation rates in the metaanalysis were comparable between tofacitinib and other bDMARD. Overall, neither our study nor the metaanalysis showed an advantage in terms of persistence for new users of tofacitinib. Among patients in the metaanalysis who switched after an inadequate response to a bDMARD, discontinuation rates were lower in switchers to bDMARD than in those who switched to tofacitinib. These pooled findings contradict our results. The differences may indicate selection bias or residual confounding in our data but could also be the result of differences between the study populations in RCT

Table 2. Persistence in new users of tofacitinib and bDMARD.

	Discontinued/Switched During Follow-up, n (%)	Median Persistence†	HR (Tofacitinib to the bDMARD)* Crude	Adjusted
Tofacitinib, n = 1031	591 (57.3)	0.81 (0.73–0.91)	NA	NA
bDMARD, n = 17,803	9338 (52.5)	1.02 (0.99–1.05)	1.18 (1.09–1.28)	1.14 (1.05–1.25)
Adalimumab, n = 6007	3213 (53.5)	1.00 (0.94–1.06)	1.17 (1.07–1.28)	1.13 (1.03–1.24)
Certolizumab pegol, n = 646	404 (62.5)	0.67 (0.57–0.77)	0.87 (0.76–0.98)	0.84 (0.74–0.96)
Etanercept, n = 6558	3416 (52.1)	1.03 (0.99–1.09)	1.19 (1.09–1.30)	1.17 (1.07–1.28)
Golimumab, n = 751	370 (49.3)	1.18 (0.92–1.40)	1.34 (1.18–1.53)	1.31 (1.14–1.49)
Infliximab, n = 1597	754 (47.2)	1.42 (1.23–1.67)	1.43 (1.28–1.59)	1.37 (1.22–1.53)
Abatacept, n = 1641	854 (52.0)	0.93 (0.82–1.10)	1.10 (0.99–1.22)	1.08 (0.97–1.20)
Tocilizumab, n = 603	327 (54.2)	0.82 (0.69–0.96)	0.97 (0.85–1.11)	0.96 (0.84–1.10)

* HR for discontinuation (95% CI), where the bDMARD is the reference. Values < 1 favor tofacitinib (i.e., longer persistence with tofacitinib). † Median persistence (95% CI) estimated in years using Kaplan-Meier methodology. bDMARD: biological disease-modifying antirheumatic drug; NA: not applicable.

Table 3. Persistence in switchers to tofacitinib and bDMARD.

	Discontinued/ Switched During Follow-up, n (%)	Median Persistence†	HR (Tofacitinib to the bDMARD)* Crude	Adjusted
Tofacitinib, n = 1535	815 (53.1)	1.04 (0.94–1.19)	NA	NA
bDMARD, n = 9849	5546 (56.3)	0.83 (0.78–0.86)	0.90 (0.83–0.97)	0.90 (0.83–0.97)
Adalimumab, n = 2343	1396 (59.6)	0.71 (0.67–0.77)	0.81 (0.75–0.89)	0.81 (0.74–0.89)
Certolizumab pegol, n = 746	466 (62.5)	0.64 (0.53–0.71)	0.72 (0.65–0.81)	0.72 (0.64–0.81)
Etanercept, n = 1562	916 (58.6)	0.71 (0.65–0.82)	0.82 (0.75–0.90)	0.81 (0.73–0.89)
Golimumab, n = 837	430 (51.4)	1.00 (0.87–1.17)	1.04 (0.93–1.17)	1.04 (0.92–1.18)
Infliximab, n = 695	357 (51.4)	1.13 (0.97–1.49)	1.10 (0.97–1.25)	1.10 (0.97–1.25)
Abatacept, n = 2132	1154 (54.1)	0.90 (0.84–0.99)	0.96 (0.88–1.05)	0.96 (0.87–1.05)
Tocilizumab, n = 1534	827 (53.9)	0.89 (0.80–0.98)	0.96 (0.87–1.06)	0.96 (0.87–1.06)

* HR for discontinuation (95% CI), where the bDMARD is the reference. Values < 1 favor tofacitinib (i.e., longer persistence with tofacitinib). † Median persistence (95% CI) estimated in years using Kaplan-Meier methodology. bDMARD: biological disease-modifying antirheumatic drug.

and real-world settings[10,31,32]. In a single real-world study of new users, similar discontinuation rates were reported after 1 year of treatment with tofacitinib, ETN, and ADA[33], but we found no study that tested for the difference in persistence between new users of tofacitinib and new users of bDMARD. A few studies on switchers indicated that discontinuation of tofacitinib was comparable to that of CZP[34], ADA, ETN, or ABA[35].

Our findings of longer persistence in switchers to tofacitinib compared with new users of the medication are inconsistent with the results of a small cohort study (of short duration) that compared new users of tofacitinib with switchers[36]. In that study, adverse events were comparable between new users and switchers, but the clinical effectiveness of tofacitinib for new users was better than it was for switchers to tofacitinib. These results imply longer persistence in new users of tofacitinib compared with switchers, as was observed in a recent Canadian study[37]. The longer persistence in switchers to tofacitinib in our study may have been because tofacitinib was often prescribed as a "last resort" medication, especially during the drug's first years on the market. As such, and in the absence of alternatives, patients may have persisted longer in taking tofacitinib. Our study and others in the literature support this explanation, as shown by the larger proportion of patients who tried more than 1 type of bDMARD before switching to tofacitinib compared with the relatively smaller proportion of switchers to another bDMARD[37,38].

It is likely that the shorter persistence in new users of tofacitinib is driven mainly by the large proportion of patients who did not renew their treatment after a single dispensation. In the absence of information on the causes of discontinuing the medications, we could not provide further explanation for this observation. Previous cohort studies reported discontinuation due to adverse events in 3.2–24.3% of the patients who were followed for 6–22 months[39,40,41,42,43,44]. In those studies, 1.6–20.8% of tofacitinib users discontinued their treatment due to a lack/loss of efficacy. The 2 largest studies were conducted in Japan and included 2387 and 3929 tofacitinib users. The studies reported that similar proportions of patients (approximately 9%) discontinued their treatment due to adverse events and lack of effectiveness[40,44]. Due to the nature of administrative data, we were unable to differentiate between the different reasons for discontinuing use of tofacitinib or bDMARD.

Table 4. Results of additional analysis in users of tofacitinib and bDMARD.

Description of Analysis	Tofacitinib N	Tofacitinib Median Persistence†	bDMARD N	bDMARD Median Persistence†	HR (Tofacitinib to the bDMARD)* Crude	HR (Tofacitinib to the bDMARD)* Adjusted
New users						
Medication-free gap of 90 days	1031	0.81 (0.73–0.91)	17,803	1.02 (0.99–1.05)	1.18 (1.09–1.28)	1.14 (1.05–1.25)
At least 2 prescriptions and a medication-free gap of 90 days	805	1.23 (1.00–1.43)	14,826	1.29 (1.24–1.34)	1.02 (0.93–1.13)	0.99 (0.89–1.10)
Medication-free gap of 60 days	1028	0.82 (0.73–0.91)	17,703	1.02 (0.99–1.05)	1.18 (1.09–1.28)	1.14 (1.04–1.24)
Medication-free gap of 180 days	1027	0.81 (0.72–0.90)	18,147	1.02 (0.99–1.05)	1.18 (1.08–1.28)	1.13 (1.04–1.24)
No concomitant MTX‡	541	0.72 (0.60–0.83)	6899	0.92 (0.87–0.96)	1.15 (1.03–1.29)	1.14 (1.004–1.28)
Switchers						
Medication-free gap of 90 days	1535	1.04 (0.94–1.19)	9849	0.83 (0.78–0.86)	0.90 (0.83–0.97)	0.90 (0.83–0.97)
At least 2 prescriptions and a medication-free gap of 90 days	1264	1.42 (1.26–1.63)	8391	0.98 (0.93–1.02)	0.79 (0.73–0.86)	0.81 (0.74–0.88)
Medication-free gap of 60 days	1538	1.04 (0.93–1.18)	9803	0.83 (0.78–0.86)	0.90 (0.84–0.97)	0.90 (0.83–0.97)
Medication-free gap of 180 days	1537	1.04 (0.09–1.18)	9756	0.83 (0.78–0.86)	0.90 (0.86–0.97)	0.90 (0.83–0.97)
No concomitant MTX	847	0.90 (0.75–1.04)	4684	0.77 (0.73–0.83)	0.96 (0.87–1.06)	0.94 (0.84–1.05)

* HR for discontinuation (95% CI), where the bDMARD is the reference. Values < 1 favor tofacitinib (i.e., longer persistence with tofacitinib). † Median persistence (95% CI) estimated in years using Kaplan-Meier methodology. ‡ No MTX treatment was defined as no dispensation or medical code for MTX in the 6 months before, and including, cohort entry. It is used as a proxy for patients who are intolerant of this medication. bDMARD: biological disease-modifying antirheumatic drug; MTX: methotrexate.

Table 5. Persistence by level of historical adherence.*

Cohort	No. Prescription/ Injections	Adherence Level to Oral Medications	Adjusted HR (Tofacitinib to the bDMARD)†	Adherence Level to Injectable Medications	Adjusted HR (Tofacitinib to the bDMARD)†
New users	≥ 1	High	0.95 (0.83–1.08)	High	1.22 (0.90–1.66)
		Low	1.33 (1.17–1.52)	Low	1.18 (0.84–1.66)
	≥ 2	High	0.82 (0.70–0.96)	High	0.88 (0.60–1.30)
		Low	1.15 (0.98–1.35)	Low	1.02 (0.65–1.56)
Switchers	≥ 1	High	0.86 (0.77–0.97)	High	0.91 (0.80–1.04)
		Low	0.91 (0.80–1.02)	Low	0.86 (0.73–1.02)
	≥ 2	High	0.86 (0.77–0.96)	High	0.76 (0.67–0.86)
		Low	0.88 (0.79–0.99)	Low	0.85 (0.74–0.98)

*HR are not shown for patients with unknown adherence; those patients were not treated with antirheumatic, antihypertensive, and/or oral antidiabetic medications in the 2 years before cohort entry or had a single prescription for each medication. † HR for discontinuation (95% CI), where the bDMARD is the reference. HR of discontinuation of tofacitinib compared with bDMARD were estimated from Cox regression models with an interaction term between medication and adherence level. Discontinuation was assigned based on a medication-free interval of 90 days or on switching. Values < 1 favor tofacitinib (longer persistence). bDMARD: biological disease-modifying antirheumatic drug.

Administrative data have a number of limitations. Unmeasured confounding is a potential issue in the absence of direct clinical measures such as disease severity scores. To minimize this problem, we included proxies of disease severity in the hdPS. Patient behavior, especially adherence, is also a potential confounder if treatment was selected based on this behavior. To minimize this problem, we measured patient adherence to an earlier treatment and controlled for it in our regression. Also, there are several concerns about the accuracy of measuring persistence. First, adherence during the implementation phase was strongly associated with persistence as measured in our study. Patients were more likely to be assigned "discontinuation" if their adherence was low and they had long gaps between prescription refills. Tofacitinib users had better adherence than bDMARD users; hence, they were less likely to be assigned "discontinuation." This may bias the results toward the null in new users and away from the null in switchers. Second, it is possible that not all medications dispensed were actually taken. Robust results from the analysis of patients who received at least 2 prescriptions/doses and were therefore more likely to use the medications, increased our confidence in the results. Last, in the absence of information on duration of treatment for some administration events, we used a conservative approach to impute these data based on the longest interdose interval mentioned in the product monographs. This resulted in an overestimation of persistence for some patients who were treated with most bDMARD. This may bias the results away from the null in new users and toward the null in switchers.

In conclusion, in the treatment of RA, tofacitinib was associated with shorter persistence in new users and longer persistence in switchers compared with bDMARD. Channeling based on adherence did not explain the differences between the cohorts. Further research is warranted to understand the reasons for discontinuation of tofacitinib despite its ease of administration and to understand the observed differences between switchers and new users.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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APPENDIX 1. The Canadian Network for Observational Drug Effect Studies (CNODES) investigators are Samy Suissa (principal investigator); Colin R. Dormuth (British Columbia); Brenda R. Hemmelgarn (Alberta); Gary F. Teare and Jaqueline Quail (Saskatchewan); Patricia Caetano and Dan Chateau (Manitoba); David A. Henry and J. Michael Paterson (Ontario); Jacques LeLorier (Québec); Adrian R. Levy (Atlantic: NS, NL, NB, PEI); Pierre Ernst and Kristian B. Filion (UK Clinical Practice Research Datalink (CPRD); Robert W. Platt (methods); and Ingrid S. Sketris (knowledge translation).

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Editorial

Real-world Evidence Needs Careful Interpretation

Peter Nash[1]

Determination plus persistence equals achievement.
Stanley T. Crawford

The Janus kinase (JAK) inhibitors have proven to be popular across the globe for an increasing variety of autoimmune inflammatory disorders seen in rheumatology, dermatology, and gastroenterology[1]. In patients with rheumatoid arthritis (RA), market share is on the rise in many countries, with 4 or 5 JAK inhibitors available or under development, and most patient categories are comprehensively studied, such as methotrexate (MTX)-naïve, MTX-inadequate responders, biological disease-modifying antirheumatic drug (bDMARD)–inadequate responders, and monotherapy, in large randomized controlled trials (RCT) that have shown efficacy with a manageable safety profile.

It is clear, however, that the majority of patients with RA seen in clinical practice are ineligible for RCT. For example, a study of the German RABBIT registry found less than 35% of patients with RA would be eligible for an RCT[2]; therefore, real-world observational studies are important, particularly as these patients often have worse prognostic factors including more comorbidities, older age, longer disease duration, and increased number of prior DMARD use, and RCT may overestimate therapeutic effect[3]. Further, large numbers of patients followed for long periods of time are required to show rare adverse effects.

Drug persistence over time is a surrogate for continued efficacy and the absence of AE leading to discontinuation, but there are important caveats. Drug persistence is affected by many variables such as polypharmacy, age, level of self-efficacy and social support, health perception and necessity belief, increased knowledge of RA, lower levels of education and income, as well as higher drug costs[4]. In observational studies, novel therapies are subject to selection bias — the necessity of drug failure before reimbursement, dosage restrictions mandated by regulators, time entering the market, persistence with therapy in partial responders when many other therapies have failed, efficacy as monotherapy in the MTX intolerant, the effect of competitors entering the market, as well as the ramifications of drug cost.

In this issue of *The Journal*, Fisher, *et al*[5] have examined the persistence of JAK1/3 inhibitor tofacitinib in patients with RA compared to the persistence of bDMARD of a large, carefully performed, retrospective new user cohort study in a large Canadian MarketScan research database. Over a 4-year period, new users were compared and the time between treatment initiation to discontinuation or drug switch was determined. Further analysis examined post first-line therapy in patients switching to tofacitinib from a bDMARD. They concluded that new tofacitinib users had a shorter medication persistence (median 0.81 yrs) compared to bDMARD patients (median 1.02 yrs) with an HR of 1.14. However, they also concluded that patients who switch to tofacitinib from a bDMARD had the opposite effect, that is, longer persistence than patients who switched to a bDMARD (HR for discontinuation 0.90). Are these differences clinically significant? Further, shortcomings of the study include the lack of information on the causes of discontinuation as well as the percentage (16%) of patients with non-RA diagnoses, from osteoarthritis to gout, psoriasis, ankylosing spondylitis, and vasculitis.

What is the clinician to make of such studies? How complete the data integrity of the Canadian Network for Observational Drug Effect Studies is and perhaps whether data entry is voluntary or mandated are relevant. The timing of tofacitinib entry to the Canadian market in relation to bDMARD and the provincial Canadian access regulations affect rheumatologist therapeutic choice and drug persistence as does, importantly, the size of the monotherapy market where JAK inhibitors and tocilizumab have an advantage over other bDMARD.

What have similar analyses shown? Two studies[6,7] found

See Tofacitinib persistence, *page 16*

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that tofacitinib was more commonly used as monotherapy than bDMARD, and persistence in treatment and adherence were quite comparable between tofacitinib and bDMARD. Another study showed patients initiating tofacitinib had longer disease duration and at the group level had been exposed to more bDMARD than patients initiating a bDMARD[8]. The Swiss Clinical Quality Management registry, which includes almost 2000 patients initiating treatment with tofacitinib, tumor necrosis factor inhibitors (TNFi), or non-TNFi bDMARD, found similar crude drug retention rates for the 3 cohorts[9]. After adjustment, a higher risk of discontinuation was associated with TNFi versus tofacitinib (HR 1.27). A higher number of prior bDMARD and greater BMI values were significantly associated with an increased risk of discontinuation. In contrast to the findings of Fisher, *et al*, an Australian study found the median persistence of treatment for the matched population was not significantly different at 33.8 months for patients prescribed with bDMARD and at 34.2 months for patients prescribed with tofacitinib; the reasons for discontinuation in the bDMARD and tofacitinib arms, respectively, were assessed as completion of treatment (33% vs 25%), lack of efficacy (22% vs 17%), secondary failure (16% vs 10%), and adverse effects (16% vs 12%)[10]. More relevant is a Canadian study of long-term extension of clinical trials that showed median drug survival for all tofacitinib-treated patients was 4.9 years and estimated 2- and 5-year drug survival rates were 75.5% and 49.4%, respectively. Positive serology, low BMI, MTX monotherapy, or MTX dose 15 mg or less per week, and absence of specific comorbidities (diabetes, hypertension, or cardiovascular disease) appeared to be associated with increased drug survival. The most common reasons for discontinuation were adverse effects (23.9%), lack of patient willingness to participate (10.1%), "other" reasons (6.2%; i.e., any reason not otherwise classified), and lack/loss of efficacy (3.6%)[11].

In conclusion, real-world data are clinically important, and drug survival with appropriate caveats is a good surrogate for continued efficacy and lack of AE necessitating discontinuation. Studies such as those by Fisher, *et al*[5] are informative but require cautious interpretation because findings are dependent on a variety of medical and nonmedical influences. Confirmation from similar studies in large registries from a variety of countries with differing medical systems would help to clarify the picture and advise on drug persistence of any novel therapy, in this instance the first JAK inhibitor in the rheumatology market.

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