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ORIGINAL RESEARCH

Real-World Persistence with Tocilizumab Compared to Other Subcutaneous Biologic Disease-Modifying Antirheumatic Drugs Among Patients with Rheumatoid Arthritis Switching from Another Biologic

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ABSTRACT

Introduction: In patients with rheumatoid arthritis (RA) who have an inadequate response to or intolerance of their first biologic disease-modifying antirheumatic drug (bDMARD), guidelines recommend switching to a different biologic class. The objective of this study was to compare persistence with subcutaneous (SC) tocilizumab to persistence with other SC bDMARDs when these drugs are used as subsequent-line therapy in RA patients who previously received ≥ 1 bDMARD.

Methods: RA patients in a US administrative claims database who initiated a second- or subsequent-line SC bDMARD between January 1, 2012 and June 30, 2017 (initiation date = index date) were included. Persistence was defined as the number of days between the bDMARD initiation date and (1) the last supplied day of medication fill (primary) or (2) the day on which the patient switched or there was a gap in treatment of > 90 days (secondary). Parametric survival models utilizing an exponential distribution with a robust variance estimator were used to compare persistence with tocilizumab to persistence with other bDMARDs.

Results: A total of 10,301 patients with 12,704 bDMARD episodes were included. Patients receiving tocilizumab had a significantly higher adjusted median (95% CI) number of days of primary persistence [333 (311–356)] than those receiving adalimumab [280 (268–293); $P < 0.001$], certolizumab [262 (241–284); $P < 0.001$], and etanercept [289 (274–304); $P = 0.001$], and a similar persistence to those receiving abatacept [320 (305–335); $P = 0.327$] and golimumab [304 (274–333); $P = 0.122$].

Conclusion: Among patients with RA who had previously received ≥ 1 bDMARD, tocilizumab-treated patients exhibited a similar or significantly better biologic persistence than those receiving other bDMARDs.

Keywords: Biologic; Persistence; Real-world; Rheumatoid arthritis; Tocilizumab

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Key Summary Points

Why carry out this study?

In patients with rheumatoid arthritis (RA) who have an inadequate response to or intolerance of their first biologic disease-modifying antirheumatic drug (bDMARD), current guidelines recommend switching to a different biologic class.

The objective of this study was to compare persistence with subcutaneous (SC) tocilizumab to persistence with other SC bDMARDs when these drugs are used as subsequent-line therapy in RA patients who previously received first-line bDMARD(s).

What was learned from this study?

Among patients with RA who previously received ≥ 1 bDMARD, tocilizumab-treated patients exhibited similar or significantly better biologic persistence than those receiving other bDMARDs.

This study, which involved a large number of second- or subsequent-line SC bDMARD episodes in patients with RA across the United States, provides valuable real-world information and adds to existing data on persistence with bDMARDs.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease characterized by joint swelling, stiffness, and pain and synovial inflammation, which can lead to permanent joint damage and disability if left untreated [1, 2]. The goal of RA treatment is to achieve sustained remission or low disease activity based on shared decision-making between the patient and rheumatologist taking into account disease activity, prognostic factors, and comorbidities [2–4]. The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines recommend that RA should initially be treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate [2, 3]. If patients have an inadequate response to csDMARDs, the addition of either a second csDMARD, a biologic DMARD (bDMARD), or a targeted synthetic DMARD is recommended [2, 3].

Although bDMARDs are effective for many patients with RA, switching to another biologic may sometimes be necessary because of treatment-related adverse events or a failure to achieve adequate disease control [5]. Approximately 30–40% of patients have an inadequate response to csDMARDs and first-line bDMARDs, most commonly tumor necrosis factor inhibitors (TNFis) [6–8]. In addition, patients receiving bDMARDs may experience a loss of response to treatment over time [9]. In patients with RA who have an inadequate response to or are intolerant of their first bDMARD, guidelines recommend switching to a different biologic class or a targeted synthetic DMARD [2, 3]. Understanding persistence with subsequent-line biologic therapies is important, as it can help to guide rheumatologists and patients in choosing an appropriate therapy after an inadequate response to or intolerance of first-line biologics.

Approved biologics for use in patients with RA have different mechanisms of action, and although there is evidence that supports switching to a biologic with a different mechanism of action, switching to another TNFi is more common in clinical practice [10, 11]. However, the ACR guidelines recommend switching to a non-TNFi after a first-line TNFi failure [2]; additionally, treatment patterns of switching to a bDMARD with a different mechanism of action in patients in whom a first-line bDMARD has failed are increasing. If a patient has an inadequate response to a second bDMARD, multiple guidelines recommend that they should be switched to a biologic with a different mechanism of action [2, 3].

Currently available subcutaneous (SC) bDMARDs include TNFis (adalimumab, certolizumab, etanercept, and golimumab), abatacept (a T-cell costimulation inhibitor), interleukin (IL)-6 receptor blockers (tocilizumab and sarilumab), and the IL-1 receptor

antagonist (anakinra). Treatment persistence has been associated with improved outcomes in patients with RA [12]. However, real-world studies of persistence with SC bDMARDs and comparative information on persistence with SC bDMARDs among patients with RA who are not biologic naïve are limited. The objective of this study was to compare persistence with SC-administered tocilizumab to persistence with other SC bDMARDs when these drugs were used as subsequent-line therapy in RA patients who previously responded inadequately to or were intolerant of first-line bDMARDs.

METHODS

Data Source and Patient Population

This US-based retrospective observational study used medical claims data from the IBM® MarketScan® Commercial and Medicare Supplemental Databases, which provide detailed costs, use, and outcomes data for healthcare services performed in both inpatient and outpatient settings. Adult patients (aged 18–89 years) with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or ICD-10-CM diagnosis of RA who initiated a SC bDMARD between January 2, 2012 and June 30, 2017 were identified. The index date was defined as the date of SC bDMARD initiation.

Patients were included if they were continuously enrolled in a commercial or Medicare plan for $\geq$ 6 months before and $\geq$ 3 months after the index date; had received any prior bDMARD, including those not evaluated in this analysis; and did not have other autoimmune conditions during the study period, including ankylosing spondylitis, Crohn's disease, ulcerative colitis, polyarteritis nodosa, granulomatosis with polyangiitis, systemic lupus erythematosus, non-Hodgkin's lymphoma, plaque psoriasis, psoriatic arthritis, and juvenile idiopathic arthritis.

This retrospective, observational analysis used only de-identified patient records and did not include the collection, use, or transmittal of individually identifiable data; therefore, institutional review board approval to conduct this study was not necessary.

Covariates

Factors evaluated for persistence included age, sex, geographic region, health plan type, Elixhauser Comorbidity Index (ECI) score [13–15], initial bDMARD, line of biologic therapy (e.g., second, third, etc.), and year of starting the bDMARD. Patients' comorbidities, as identified by ECI, were carried forward from prior treatment episodes if the patients had $\geq$ 1 episode.

Outcomes

Primary bDMARD persistence was defined as the number of days between the initiation date and the last supplied day of medication fill. Patients who had a gap in therapy (e.g., during a period of remission) and then restarted on the same bDMARD were considered to be persistent; patients who switched therapy were considered nonpersistent [16]. Secondary persistence was defined as the period of time that patients received bDMARDs until they switched or had a gap in treatment of $>$ 90 days [16]. Patients who switched to a different bDMARD were included as a separate episode (i.e., patients could have multiple episodes due to switching to a different biologic as a third- or subsequent-line therapy). For patients who had a gap in treatment of $>$ 90 days and then restarted the same bDMARD, only the episode prior to the 90-day gap was included in the analysis.

Statistical Analysis

Analysis of variance and χ^2 tests were used to compare demographic and clinical characteristics between bDMARD episodes. Parametric survival models utilizing an exponential distribution with a robust variance estimator were used to compare outcomes with tocilizumab to those with other bDMARDs, adjusting for differences in baseline characteristics and comorbidities over time prior to initiating subsequent bDMARDs and accounting for correlation among different bDMARD episodes. Hazard ratios for discontinuation were derived from the survival models after adjusting for patients' baseline demographics, lines of therapy, and episode-specific comorbidities.

Patients who left the database (e.g., patients who died or switched to a health plan outside of the database) were censored.

RESULTS

Demographics and Baseline Characteristics

Overall, 10,301 patients with 12,704 bDMARD episodes were included (Fig. 1). The most common bDMARD episode was adalimumab (n = 3599), followed by abatacept (n = 2988), etanercept (n = 2760), tocilizumab (n = 1630), golimumab (n = 745), and certolizumab pegol (n = 982). Most patients were female (78.9–82.2%), and mean age ranged from 51.0 to 53.2 years (Table 1). Mean [SD] ECI scores were significantly higher ($P < 0.001$) in patients initiating tocilizumab (2.8 [2.3]) than in those receiving abatacept (2.5 [2.2]), adalimumab (2.5 [2.1]), certolizumab pegol (2.4 [2.0]), etanercept (2.4 [2.0]), or golimumab (2.4 [2.2]) (Table 1).

Outcomes

Tocilizumab was the least frequently used second-line bDMARD and the most frequently used third-, fourth-, and fifth-line bDMARD (Fig. 2). The adjusted median (95% CI) number

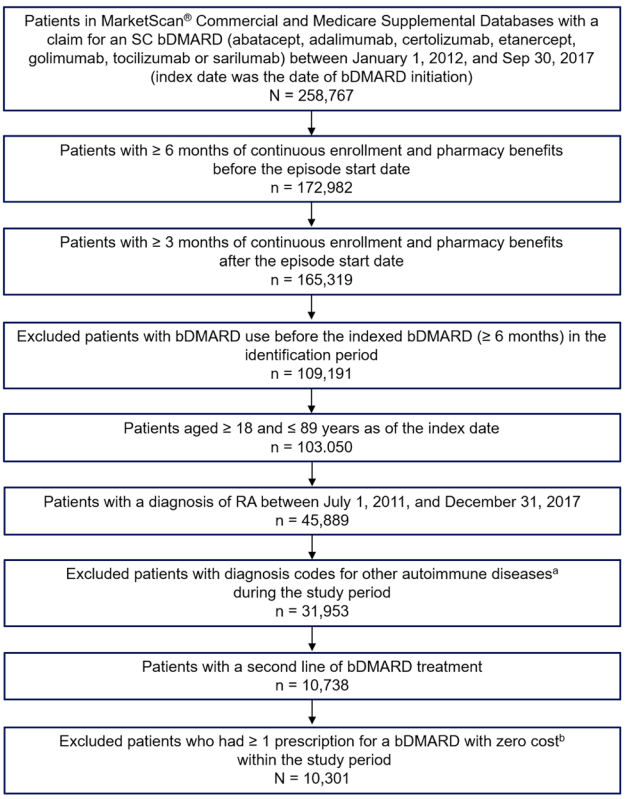


Fig. 1 Patient attrition

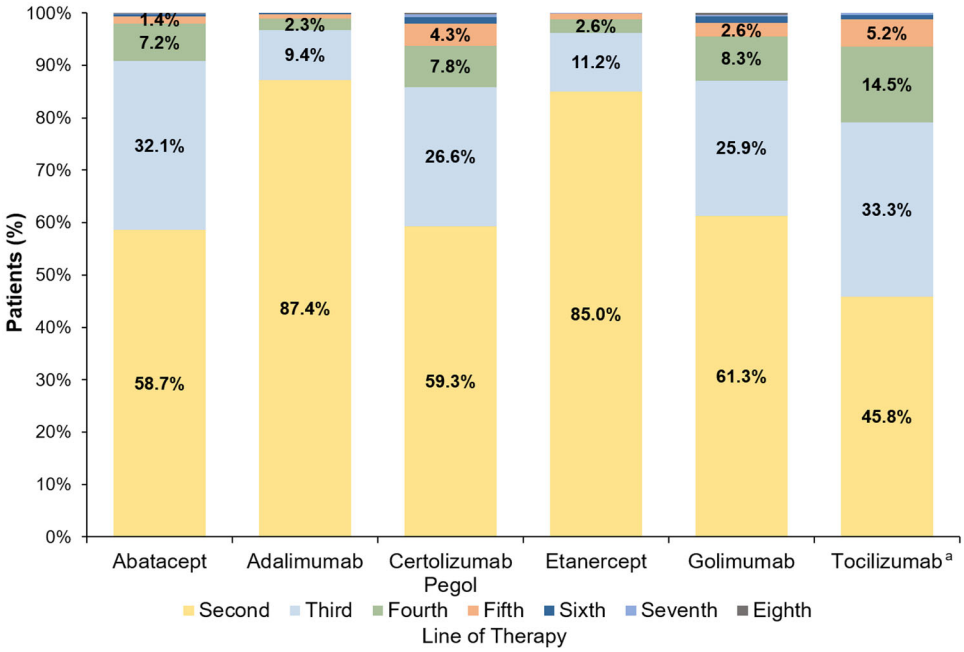
Table 1 Demographics and characteristics

Variable	Abatacept *n* = 2988	Adalimumab *n* = 3599	Certolizumab pegol *n* = 982	Etanercept *n* = 2760	Golimumab *n* = 745	Tocilizumab *n* = 1630	*P* value[a]
Age, mean (SD)	53.2 (11.0)	52.7 (11.3)	51.0 (11.0)	52.5 (10.9)	52.1 (11.2)	52.7 (10.6)	< 0.001
Female, *n* (%)	2446 (81.9)	2838 (78.9)	807 (82.2)	2206 (79.9)	610 (81.9)	1325 (81.3)	0.018
Health plan type, *n* (%)							
HMO	269 (9.00)	338 (9.39)	81 (8.25)	252 (9.13)	67 (8.99)	117 (7.18)	0.169
PPO	2017 (67.5)	2391 (66.4)	692 (70.5)	1878 (68.0)	500 (67.1)	1122 (68.8)	0.196
Other	702 (23.5)	870 (24.2)	209 (21.3)	630 (22.8)	178 (23.9)	391 (24.0)	0.472
US region, *n* (%)							
Northeast	539 (18.0)	620 (17.2)	131 (13.3)	443 (16.1)	136 (18.3)	271 (16.6)	0.013
South	1271 (42.5)	1564 (43.5)	519 (52.9)	1327 (48.1)	292 (39.2)	735 (45.1)	0
North Central	616 (20.6)	737 (20.5)	157 (16.0)	496 (18.0)	146 (19.6)	307 (18.8)	0.005
West	535 (17.9)	631 (17.5)	170 (17.3)	467 (16.9)	152 (20.4)	292 (17.9)	0.392
Unknown	27 (0.9)	47 (1.3)	5 (0.5)	27 (1.0)	19 (2.6)	25 (1.5)	0.001
ECI score, mean (SD)	2.5 (2.2)	2.5 (2.1)	2.4 (2.0)	2.4 (2.0)	2.4 (2.2)	2.8 (2.3)	< 0.001
Comorbidities, *n* (%)							
Chronic pulmonary disease	486 (16.3)	503 (14.0)	126 (12.8)	386 (14.0)	118 (15.8)	284 (17.4)	0.001
Deficiency anemias	426 (14.3)	448 (12.4)	131 (13.3)	369 (13.4)	98 (13.2)	251 (15.4)	0.077
Depression	279 (9.34)	371 (10.3)	80 (8.1)	265 (9.6)	65 (8.7)	175 (10.7)	0.185
Diabetes without chronic complications	379 (12.7)	446 (12.4)	94 (9.6)	304 (11.0)	87 (11.7)	202 (12.4)	0.072
Fluid and electrolyte disorders	233 (7.8)	232 (6.4)	74 (7.5)	187 (6.8)	51 (6.8)	130 (8.0)	0.211
Hypothyroidism	513 (17.2)	575 (16.0)	161 (16.4)	458 (16.6)	117 (15.7)	327 (20.1)	0.010
Liver disease	149 (5.0)	154 (4.3)	50 (5.1)	125 (4.5)	30 (4.0)	82 (5.0)	0.613
Obesity	487 (16.3)	613 (17.0)	180 (18.3)	470 (17.0)	116 (15.6)	332 (20.4)	0.009
Hypertension	1070 (35.8)	1316 (36.6)	346 (35.2)	978 (35.4)	269 (36.1)	638 (39.1)	0.184
RA/collagen vascular disease	2273 (76.1)	2731 (75.9)	765 (77.9)	2071 (75.0)	570 (76.5)	1342 (82.3)	< 0.001
Valvular disease	130 (4.4)	131 (3.6)	40 (4.1)	93 (3.4)	28 (3.8)	81 (5.0)	0.103

ECI Elixhauser Comorbidity Index, *HMO* health maintenance organization, *PPO* preferred provider organization, *RA* rheumatoid arthritis

[a] $P < 0.05$ indicates a statistically significant difference among therapies

of days of primary persistence for tocilizumab [333 (311–356)] was significantly higher than those for adalimumab [280 (268–293); $P < 0.001$], certolizumab [262 (241–284); $P < 0.001$], and etanercept [289 (274–304); $P = 0.001$], and similar to those for abatacept



bDMARD biologic disease-modifying antirheumatic drug

[a] $P < 0.001$ for comparison between therapies

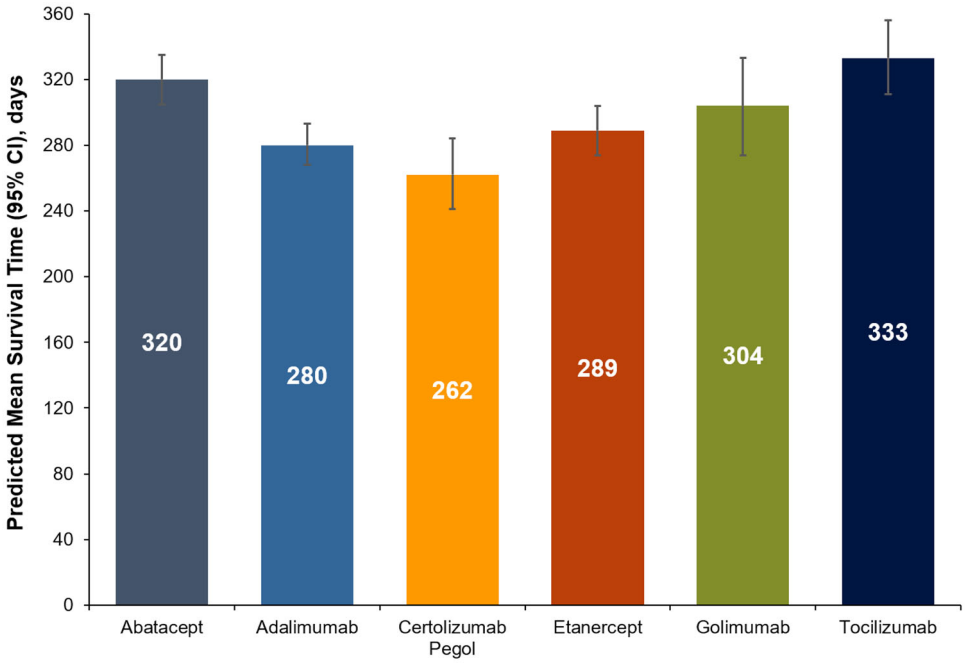
Fig. 2 Lines of bDMARD therapy by biologic

[320 (305–335); $P = 0.327$] and golimumab [304 (274–333); $P = 0.122$] (Fig. 3). The adjusted median (95% CI) number of days of secondary persistence for tocilizumab [315 (292–337)] was significantly higher than those for adalimumab [265 (253–276); $P < 0.001$], certolizumab pegol [253 (231–275); $P < 0.001$], and etanercept [272 (257–286); $P = 0.001$], and similar to those for abatacept [306 (291–321); $P = 0.545$] and golimumab [284 (257–311); $P = 0.092$] (Fig. 4). After adjusting for patients' baseline demographics, lines of therapy, and episode-specific comorbidities, adalimumab, certolizumab pegol, and etanercept had significantly higher likelihoods of discontinuation than tocilizumab (Tables 2, 3).

Among the patients who received tocilizumab for ≥ 12 months, 45% initiated tocilizumab administered every other week (q2w) and 55% initiated tocilizumab weekly (qw). Of the 347 patients who initiated q2w tocilizumab, 32.8% switched to qw dosing over the 12-month follow-up; the mean time to switch was 177 days. After 12 months of follow-up, approximately 68.3% of patients were receiving qw dosing and 31.7% were receiving q2w dosing.

DISCUSSION

In this large US claims-based analysis, persistence with tocilizumab as a second- or subsequent-line bDMARD in patients with RA was found to be similar to or significantly longer than persistence with other bDMARDs. These results are consistent with registry studies showing increased persistence with tocilizumab compared to persistence with TNFis in patients who had an inadequate response to a first-line TNFi [17–19]. Although the present study did not evaluate the reasons for patients switching or discontinuing bDMARD therapy, previous studies have shown that multiple factors are both positively and negatively associated with persistence, including age, sex, and race, as well as disease activity, comorbidities, concurrent use of methotrexate, and therapy-management programs [20].



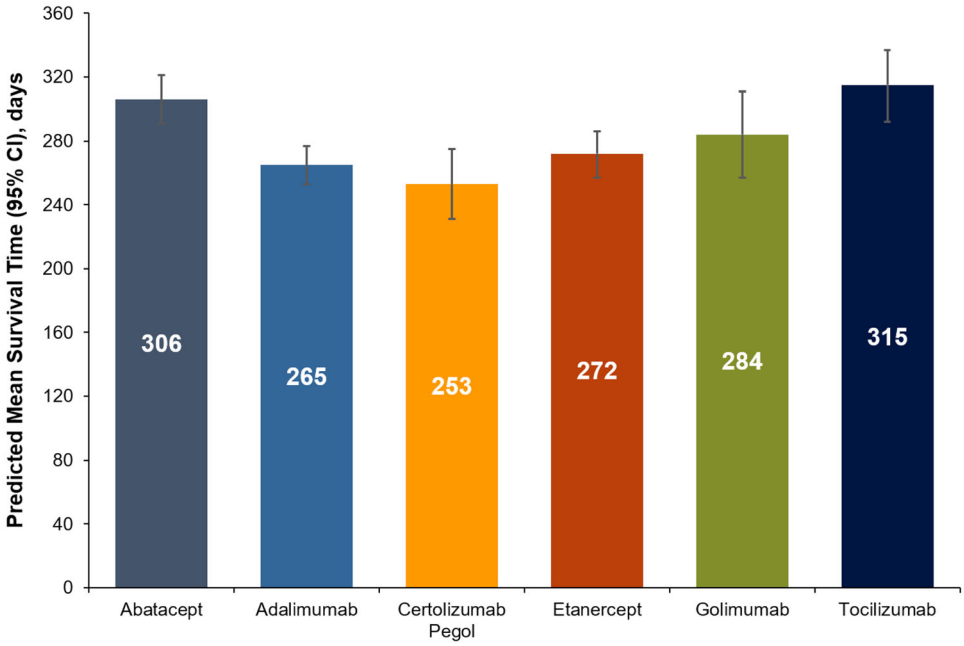
bDMARD biologic disease-modifying antirheumatic drug, *RA* rheumatoid arthritis

[a] Primary persistence was defined as the number of days between initiation date and last supplied date of biologic medication fill. The adjusted means were derived from the survival models after adjusting for patients' baseline demographics, lines of therapy and episode specific comorbidities

Fig. 3 Adjusted mean primary persistence with bDMARDs among patients with RA[a]

The intravenous and SC formulations of tocilizumab have been shown to be safe and effective treatments for patients with RA who are bDMARD naïve and for those with prior exposure to bDMARDs, either as a monotherapy or in combination with csDMARDs [21–25]. As shown in the present study, patients (particularly those treated with tocilizumab) may receive third, fourth, or greater lines of biologic therapy. Frequent switching of biologic therapy can make longer-term management of RA more challenging (e.g., management by payers requiring step therapy) and result in greater costs [26]. Studies have shown that switching from a TNFi to a biologic with a different mechanism of action can be more effective (e.g., higher persistence, improved clinical outcomes) than switching to another TNFi [11, 27–32]. Results from the present study also suggest that for patients who have an inadequate response to their first biologic, switching to one with a different mechanism of action may be more effective than switching to another biologic with the same mechanism of action.

Lower costs have been reported in patients who switched to a bDMARD with a different mechanism of action [28]. Another study reported higher direct costs but lower indirect costs in patients who switched from a first-line TNFi to a bDMARD with a different mechanism of action than in those who switched to another TNFi [33]. For patients weighing < 100 kg, tocilizumab SC is initiated q2w, followed by an increase to qw based on clinical response; for patients weighing > 100 kg, SC tocilizumab is initiated qw [34]. In the present study, 33% of patients increased tocilizumab dosing from q2w to qw. These results are consistent with a long-term study of SC tocilizumab which showed that 23% of patients who initiated SC TCZ q2w injections switched to qw within 2 years; in the patients who switched to qw dosing,



bDMARD biologic disease-modifying antirheumatic drug, *RA* rheumatoid arthritis.

[a] Secondary persistence was defined as the time patients were receiving bDMARDs until they switched or had a gap > 90 days. The adjusted means were derived from the survival models after adjusting for patients' baseline demographics, lines of therapy and episode specific comorbidities

Fig. 4 Adjusted mean secondary persistence with bDMARDs among patients with RA[a]

Table 2 Risk of discontinuing bDMARDs vs. tocilizumab for primary persistence

	Abatacept *n* = 2988	**Adalimumab *n* = 3599**	**Certolizumab pegol *n* = 982**	**Etanercept *n* = 2760**	**Golimumab *n* = 745**	**Tocilizumab *n* = 1630**
Hazard ratio	1.04	1.19	1.27	1.15	1.10	Reference
(95% CI)[a]	(0.96–1.13)	(1.10–1.29)	(1.14–1.41)	(1.06–1.26)	(0.98–1.24)	

bDMARD biologic disease-modifying antirheumatic drug

[a] Hazard ratios were derived from the survival models after adjusting for patients' baseline demographics, lines of therapy, and episode-specific comorbidities

Table 3 Risk of discontinuing bDMARDs vs. tocilizumab for secondary persistence

	Abatacept *n* = 2988	**Adalimumab *n* = 3599**	**Certolizumab pegol *n* = 982**	**Etanercept *n* = 2760**	**Golimumab *n* = 745**	**Tocilizumab *n* = 1630**
Hazard ratio	1.03	1.19	1.24	1.16	1.11	Reference
(95% CI)[a]	(0.94–1.12)	(1.09–1.29)	(1.12–1.39)	(1.06–1.27)	(0.98–1.25)	

bDMARD biologic disease-modifying antirheumatic drug

[a] Hazard ratios were derived from the survival models after adjusting for patients' baseline demographics, lines of therapy, and episode-specific comorbidities

improvements in ACR response and DAS28 remission were achieved [22]. The flexibility to increase dosing based on clinical response may contribute to the longer persistence observed with tocilizumab.

Limitations

The results of this analysis may not be generalizable to all patients with RA, including those who do not have health insurance. Drug samples provided to the patient by their doctor and prescriptions filled in situations where the patient does not use their prescription drug coverage are not captured in the pharmacy claims data in the MarketScan databases. Finally, a substantial proportion of tocilizumab use (45.8%) was as a second-line bDMARD, but some patients also received tocilizumab as a third-line (33.3%) or subsequent-line bDMARD. Thus, one should also consider the possibility that persistence was longer in this group of patients because fewer options for subsequent therapies were available to them. However, the analysis was adjusted for line of therapy, and an increasing number of biologic therapies are available for patients, so we do not believe that this had an effect on persistence.

Despite the abovementioned limitations, this study involving a large number of second- or subsequent-line SC bDMARD episodes in patients with RA across the United States provides valuable real-world information and adds to the existing data on persistence with bDMARDs.

CONCLUSIONS

Among patients with RA who previously received ≥ 1 other bDMARD, those who received tocilizumab exhibited similar or significantly better persistence than those receiving other bDMARDs.

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Compliance with Ethics Guidelines. This retrospective, observational analysis used only de-identified patient records and did not include the collection, use, or transmittal of individually identifiable data; therefore, institutional review board approval to conduct this study was not necessary.

Data Availability. The database used for the analyses in this paper is commercially available from IBM Watson at https://www.ibm.com/watson-health/learn/truven-health-analytics. The license agreement to access these data does not give the authors permission to share this database.

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