Treatment Persistence and Clinical Outcomes of Tumor Necrosis Factor Inhibitor Cycling or Switching to a New Mechanism of Action Therapy: Real-world Observational Study of Rheumatoid Arthritis Patients in the United States with Prior Tumor Necrosis Factor Inhibitor Therapy

Wenhui Wei · Keith Knapp · Li Wang · Chieh-I Chen · Gary L. Craig · Karen Ferguson · Sergio Schwartzman

ABSTRACT

Introduction: To examine treatment persistence and clinical outcomes associated with switching from a tumor necrosis factor inhibitor (TNFi) to a medication with a new mechanism of action (MOA) (abatacept, anakinra, rituximab, tocilizumab, or tocicyitinib) versus cycling to another TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) among patients with rheumatoid arthritis.

Methods: This retrospective, longitudinal study included patients with rheumatoid arthritis in the JointMan® US clinical database who received a TNFi in April 2010 or later and either cycled to a TNFi or switched to a new MOA therapy by March 2015. Cox proportional hazards models were used for time to non-persistence (switching or discontinuing). An ordinary least squares regression model compared 1-year reduction from baseline for the Clinical Disease Activity Index (CDAI).

Results: There were 332 (54.2%) TNFi cyclers and 281 (45.8%) new MOA switchers. During a median follow-up of 29.9 months, treatment persistence was 36.7% overall. Compared with new MOA switchers, TNFi cyclers were 51% more likely to be non-persistent (adjusted hazard ratio, 1.511; 95% CI 1.196, 1.908), driven by a higher likelihood of switching again (adjusted hazard ratio, 2.016; 95% CI 1.428, 2.847). Clinical outcomes were evaluable for 239 (53.3%) TNFi cyclers and 209 (46.7%) new MOA switchers. One-year mean reduction in CDAI from baseline to end of follow-up was significantly higher for new MOA switchers than TNFi cyclers (−7.54 vs. −4.81; P = 0.037), but the difference was not statistically significant after adjustment for baseline CDAI (−6.39 vs. −5.83; P = 0.607).

Conclusion: In this study, TNFi cycling was common in clinical practice, but switching to a new MOA DMARD was associated with significantly better treatment persistence and a trend toward greater CDAI reduction that was not significant after adjustment for baseline disease activity.
INTRODUCTION

Approximately 1.5 million US adults have rheumatoid arthritis (RA) [1]. The total annual societal cost of RA in the US is estimated to be approximately $39 billion, including $8 billion of direct healthcare costs, $11 billion of indirect healthcare costs such as work and productivity loss, and $20 billion of intangible costs such as decreased quality of life and premature mortality [2].

RA is a chronic, inflammatory, autoimmune disease characterized by joint swelling, tenderness, and destruction [3]. Conventional synthetic disease-modifying antirheumatic drugs (cDMARDs), including methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide, are the standard of care for RA [4–6]. Treatment with a tumor necrosis factor inhibitor (TNFi), such as adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab, or other biologic agents and small molecules is recommended for RA patients with moderate or high disease activity despite treatment with one or more cDMARDs [6]. However, many RA patients do not benefit from or tolerate the initial TNFi therapy, or they lose response over time [7, 8]. Several trials and observational studies have reported that clinical outcomes may improve after patients switch to either another TNFi (TNFi cycling) or to a therapy with a new mechanism of action (new MOA switching) such as abatacept, anakinra, rituximab, tocilizumab, or tofacitinib [9–18]. Recent changes in the American College of Rheumatology’s RA treatment guidelines now give new MOA therapies the same priority as TNFi when selecting therapy in patients with established disease [6].

METHODS

Data Source

This retrospective, observational study used the US clinical database JointMan® (Discus Analytics, LLC, Spokane, WA, USA), a rheumatology software application that systematically collects real-world data for rheumatology practices. At each patient encounter, the provider uses JointMan to record diagnoses, medications, and laboratory results, including the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). A color-coded anatomical diagram (homunculus) is used to record the presence or absence of tenderness, swelling, deformity, or decreased range of motion for each joint (Fig. 1). Radiographic data are not available in the database. No identifiable protected health information was extracted or accessed during the study, pursuant to the US Health Insurance Portability and Accountability Act. Because the study did not involve the collection, use, or transmittal of individually identifiable data, and data were collected in the setting for the usual care of the patient, Institutional Review Board approval to conduct this study was not necessary.

Study Population

The study period was from 1 April 2010 through 31 March 2015. During this period, the JointMan database included more than 5800 unique patients with RA who were treated by more than 50 rheumatologists in Washington, New York, Oregon, California, and Wisconsin. Patients were included in the study if they had the following: a
provider-selected diagnosis of RA, a prescription for a TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) during the study period, and a prescription for a different TNFi or a new MOA therapy approved for RA treatment (abatacept, anakinra, rituximab, tocilizumab, or tofacitinib) during the study period and after the end date for the prior TNFi. These TNFi and new MOA therapies were available for use in the US during the study period.

The date of the first prescription for the subsequent TNFi or new MOA therapy was designated as the study index date. Patients were required to be aged 18 years or older on the study index date. To be evaluable for treatment persistence and reasons for non-persistence, patients needed at least one patient encounter post-index. To be evaluable for clinical outcomes after the study index date, patients needed at least one patient encounter post-index, at least one Clinical Disease Activity Index (CDAI) score within 6 months pre-index, and at least one CDAI score within 12 months post-index. Although patients may have been exposed to more than two TNFi or new MOA DMARDs, only the first and second therapy switches were analyzed. The first switch was at the study index date (from a TNFi to another TNFi or a new MOA DMARD), and the second switch was captured in the analysis of “switchers” post-index.

Fig. 1 The JointMan® color-coded anatomical (homunculus) diagram, tied to calculated algorithms and validated tests. Source: Ref. [43]. (Reproduced with permission from Discus Analytics LLC)
Measures

Treatment persistence for the index drug was defined as continuing the index drug, without switching or discontinuation, based on all data collected from the study index date to the end of the study period. There was no minimum or maximum limit for duration of follow-up. Switching included patients who switched again to another TNFi or new MOA therapy. Discontinuation included patients with a recorded end date for the index drug who did not switch to a different drug; this category included patients with a treatment gap who later reinitiated the index drug. In the JointMan electronic medical records, sufficient data were available to calculate scores for the following common clinical outcomes in RA: CDAI [26], Disease Activity Score with erythrocyte sedimentation rate (DAS28-ESR) [27], Disease Activity Score with C-reactive protein (DAS28-CRP) [28], and Routine Assessment of Patient Index Data 3 (RAPID3) [29].

Statistical Analysis

The TNFi cycling cohort included patients who cycled to a different TNFi on the study index date, and the new MOA switching cohort included patients who switched to a new MOA therapy on the study index date. Baseline demographic and clinical characteristics were compared between cohorts. P values were calculated with chi-square tests for categorical variables and t tests for continuous variables. Statistical significance was defined as an alpha of 0.05. Statistical analyses used SAS version 9.3 (Cary, NC, USA).

Kaplan-Meier curves were used to examine duration of treatment persistence, and the log-rank test was used to examine differences between the cohorts. Cox proportional hazards models were used to evaluate the relationship between potential predictor variables, with patient demographic and clinical characteristics as independent variables. The dependent variables were time to discontinuation, time to switching, and time to non-persistence. Independent variables were age, sex, race, geographic region, insurance type, index year, methotrexate use, route of administration for index drug, baseline CDAI score, and TNFi cycling vs. new MOA switching. Hazard ratios (HR), 95% confidence interval (CI), and P values were used to interpret the results. A subgroup analysis of 1-year treatment persistence, switching, and discontinuation rates was conducted among patients with at least 1 year of follow-up.

Clinical outcomes were measured by the 1-year reductions in CDAI from baseline and were compared between cohorts. CDAI was selected for primary outcomes instead of DAS28-ESR or DAS28-CRP because more patients had CDAI data. Baseline was the score closest to the study index date between 6 months pre-index and 1 month post-index. End of follow-up was the score closest to, but not greater than, 12 months post-index. To adjust for baseline differences, an ordinary least squares regression model compared 1-year CDAI reduction from baseline between TNFi cyclers and new MOA switchers. Baseline patient demographics and clinical conditions were added to the model as independent variables. Achievement of a minimally important difference in CDAI in each cohort was analyzed for the following subgroups according to baseline CDAI scores [30]: at least a 1-point reduction for patients with low disease activity at baseline (CDAI <10); at least a 6-point reduction for patients with moderate disease activity at baseline (CDAI 10-22); and at least a 12-point reduction for patients with high disease activity at baseline (CDAI >22). Sensitivity analyses were conducted to compare the cohorts for overall 1-year reductions from baseline for DAS28-ESR, DAS28-CRP, and RAPID3.

RESULTS

Baseline Characteristics

The 613 patients analyzed (Fig. 2) included 332 (54.2%) TNFi cyclers and 281 (45.8%) new MOA switchers (Table 1). Etanercept was the pre-index TNFi for half of the study population (50.0%), followed by adalimumab (24.3%) and
infliximab (17.4%) (Table 2). The most common TNFi that patients cycled to was adalimumab (23.0%); the most common new MOA therapy that patients switched to was rituximab (14.7%). The most commonly reported reason for stopping the prior TNFi was primary ineffectiveness (41.9%), followed by secondary loss of efficacy (19.4%) and adverse events (11.4%) (Table 1).

Similar proportions of patients who stopped the prior TNFi because of primary ineffectiveness either cycled to another TNFi or switched to a new MOA (41.0% vs. 43.1%; P = 0.600). Patients were more likely to cycle to another TNFi than to switch to a new MOA due to secondary loss of efficacy after an initial response to the prior TNFi (22.9% vs. 15.3%; P = 0.018) or due to insurance/cost reasons (6.0% vs. 2.5%; P = 0.034). Those who had adverse events with the prior TNFi were less likely to cycle to another TNFi than to switch to a new MOA (8.1% vs. 15.3%; P = 0.005). Other reasons for the change in therapy are provided in Table 1. TNFi cyclers were also significantly younger than new MOA switchers (55.1 vs. 58.1 years; P = 0.005) and less likely to be rheumatoid factor (RF) positive (63.1% vs. 72.5%; P = 0.024) or have erosions (42.3% vs. 51.3%; P = 0.042) at baseline (Table 1).

**Treatment Persistence After the Index Switch**

The median duration of follow-up after the index switch was 29.9 months (mean 30.6 months). Overall, 29.2% of patients discontinued their index drug, 34.1% switched to another drug, and 36.7% were persistent on the index drug during follow-up. Of the patients who discontinued their index drug, 31.3% subsequently reinitiated treatment with the same drug.

Kaplan-Meier analyses showed that duration of treatment persistence after the study index date was significantly longer after new MOA switching compared with TNFi cycling (Fig. 3). This was further confirmed by the results from the Cox proportional hazards model that adjusted for other factors. Compared with new MOA switchers, TNFi cyclers were 51% more likely to be non-persistent than new MOA switchers (adjusted HR = 1.511; 95% CI 1.196, 1.908) and twice as likely to switch (adjusted HR = 2.016; 95% CI 1.428, 2.847) during the follow-up period (Fig. 4).

Among patients with at least 1 year of follow-up after the initial change in therapy [TNFi cyclers, N = 279 (84.0%); new MOA switchers, N = 241 (85.8%)], the 1-year treatment persistence rate after the initial change was significantly lower among TNFi cyclers than new MOA switchers (53.4% vs. 63.1%; P = 0.026). This was driven mainly by the higher rate of switching therapy again to a third medication for TNFi cyclers compared with new MOA switchers (29.0% vs. 17.0%; P = 0.001); discontinuation rates after the initial change were similar between TNFi cyclers and new MOA switchers (17.6% vs. 19.9%; P = 0.492) (Fig. 5).

**Clinical Outcomes After the Index Switch**

Clinical outcomes were evaluable for 448 patients, including 239 (53.3%) TNFi cyclers
### Table 1 Baseline demographic and clinical characteristics

|                      | Total \(N = 613\) | TNFi cyclers \(N = 332\) | New MOA switchers \(N = 281\) | \(P\) value |
|----------------------|-------------------|---------------------------|-------------------------------|-------------|
| **Age, mean (SD)**   | 56.5 (12.8)       | 55.1 (12.1)               | 58.1 (13.4)                   | 0.005       |
| **Gender, \(n\) (%)**|                   |                           |                               |             |
| Male                 | 132 (21.5)        | 71 (21.4)                 | 61 (21.7)                     | 0.923       |
| Female               | 481 (78.5)        | 261 (78.6)                | 220 (78.3)                    | 0.923       |
| **Race, \(n\) (%)** |                   |                           |                               |             |
| White                | 508 (82.9)        | 270 (81.3)                | 238 (84.7)                    | 0.270       |
| Non-white            | 41 (6.7)          | 27 (8.1)                  | 14 (5.0)                      | 0.120       |
| Missing              | 64 (10.4)         | 35 (10.5)                 | 29 (10.3)                     | 0.929       |
| **US region, \(n\) (%)** |                 |                           |                               |             |
| West (WA, CA, OR)    | 563 (91.8)        | 306 (92.2)                | 257 (91.5)                    | 0.749       |
| East (NY, WI)        | 50 (8.2)          | 26 (7.8)                  | 24 (8.5)                      | 0.749       |
| **Primary Insurance, \(n\) (%)** |             |                           |                               |             |
| Commercial           | 438 (71.5)        | 247 (74.4)                | 191 (68.0)                    | 0.079       |
| Medicaid             | 13 (2.1)          | 7 (2.1)                   | 6 (2.1)                       | 0.982       |
| Medicare             | 162 (26.4)        | 78 (23.5)                 | 84 (29.9)                     | 0.073       |
| **Index year, \(n\) (%)** |             |                           |                               |             |
| 2010–2011            | 195 (31.8)        | 114 (34.3)                | 81 (28.8)                     | 0.144       |
| 2012–2013            | 283 (46.2)        | 149 (44.9)                | 134 (47.7)                    | 0.487       |
| 2014–2015            | 135 (22.0)        | 69 (20.8)                 | 66 (23.5)                     | 0.421       |
| **Disease activity, mean (SD)** |           |                           |                               |             |
| CDAI \( (N = 486)\) | 22.7 (13.1)       | 21.9 (12.8)               | 23.7 (13.4)                   | 0.127       |
| DAS28-ESR \( (N = 400)\) | 3.8 (1.3)   | 3.7 (1.3)                 | 3.9 (1.3)                     | 0.240       |
| DAS28-CRP \( (N = 399)\) | 3.1 (1.1)   | 3.0 (1.1)                 | 3.1 (1.1)                     | 0.465       |
| RAPID3 \( (N = 484)\) | 14.3 (5.7)       | 13.9 (5.6)                | 14.8 (5.8)                    | 0.089       |
| **Index drug, \(n\) (%)** |             |                           |                               |             |
| Monotherapy          | 228 (37.2)        | 116 (34.9)                | 112 (39.9)                    | 0.209       |
| +MTX                 | 238 (38.8)        | 136 (41.0)                | 102 (36.3)                    | 0.238       |
| +non-MTX cDMARD      | 147 (24.0)        | 80 (24.1)                 | 67 (23.8)                     | 0.942       |
and 209 (46.7%) new MOA switchers. Baseline characteristics of this population (Table 2) generally were similar to those of the overall study population, but in this population the new MOA switchers had significantly higher mean CDAI scores than TNFi cyclers at baseline (24.8 vs. 21.7; \( P = 0.013 \)).

The 1-year mean reduction in CDAI from baseline to the end of follow-up was statistically significantly higher for new MOA switchers...
Table 2 Baseline demographic and clinical characteristics of patients evaluable for clinical outcomes

|                               | Total (N = 448) | TNFi cyclers (N = 239) | New MOA switchers (N = 209) | P value |
|-------------------------------|-----------------|------------------------|-----------------------------|---------|
| **Age, mean (SD)**           | 56.6 (13.0)     | 55.0 (12.4)            | 58.4 (13.4)                 | 0.006   |
| **Gender, n (%)**            |                 |                        |                             |         |
| Male                          | 88 (19.6)       | 49 (20.5)              | 39 (18.7)                   | 0.625   |
| Female                        | 360 (80.4)      | 190 (79.5)             | 170 (81.3)                  | 0.625   |
| **Race, n (%)**              |                 |                        |                             |         |
| White                         | 391 (87.3)      | 201 (84.1)             | 190 (90.9)                  | 0.031   |
| Non-white                     | 30 (6.7)        | 22 (9.2)               | 8 (3.8)                     | 0.023   |
| Missing                       | 27 (6.0)        | 16 (6.7)               | 11 (5.3)                    | 0.525   |
| **US region, n (%)**         |                 |                        |                             |         |
| West (WA, CA, OR)            | 432 (96.4)      | 232 (97.1)             | 200 (95.7)                  | 0.433   |
| East (NY, WI)                | 16 (3.6)        | 7 (2.9)                | 9 (4.3)                     | 0.433   |
| **Primary insurance, n (%)** |                 |                        |                             |         |
| Commercial                    | 293 (65.4)      | 166 (69.5)             | 127 (60.8)                  | 0.054   |
| Medicaid                      | 13 (2.9)        | 7 (2.9)                | 6 (2.9)                     | 0.971   |
| Medicare                      | 142 (31.7)      | 66 (27.6)              | 76 (36.4)                   | 0.047   |
| **Index year, n (%)**        |                 |                        |                             |         |
| 2010–2011                     | 139 (31.0)      | 79 (33.1)              | 60 (28.7)                   | 0.321   |
| 2012–2013                     | 194 (43.3)      | 101 (42.3)             | 93 (44.5)                   | 0.633   |
| 2014–2015                     | 115 (25.7)      | 59 (24.7)              | 56 (26.8)                   | 0.610   |
| **Disease activity, mean (SD)** |             |                        |                             |         |
| CDAI                          | (N = 448)       | (N = 239)              | (N = 209)                   | 0.013   |
| DAS28-ESR                     | 23.1 (13.0)     | 21.7 (12.4)            | 24.8 (13.4)                 |         |
| DAS28-CRP                     | 3.9 (1.3)       | 3.7 (1.2)              | 4.1 (1.3)                   | 0.013   |
| RAPID3                        | 3.1 (1.1)       | 3.0 (1.1)              | 3.3 (1.1)                   | 0.030   |
| **RA characteristics, n (%)** |                 |                        |                             |         |
| RF positive                   | 279 (68.4)      | 140 (64.5)             | 139 (72.8)                  | 0.073   |
| ACPA positive                 | 223 (54.7)      | 119 (54.8)             | 104 (54.5)                  | 0.937   |
| Erosions present              | 184 (45.1)      | 86 (39.6)              | 98 (51.3)                   | 0.018   |
| Joint stiffness present       | 268 (65.7)      | 149 (68.7)             | 119 (62.3)                  | 0.177   |
than TNFi cyclers (−7.54 vs. −4.81; \( P = 0.037 \)) (Table 3). Among patients with moderate (CDAI 10–22) or high (CDAI >22) disease activity at baseline, new MOA switchers were more likely than TNFi cyclers to achieve a minimally clinically important difference in CDAI, but the differences between cohorts were not statistically significant (Fig. 6). In the generalized linear model, baseline CDAI was significantly associated with change in CDAI (\( P < 0.001 \)).

New MOA switchers had greater reduction of CDAI than TNFi cyclers (−6.39 vs. −5.83), but the effect was not statistically significant (\( P = 0.607 \)).

In the sensitivity analysis of other clinical outcomes (Table 3), mean changes from baseline significantly favored new MOA switchers over TNFi cyclers for DAS28-ESR (−0.82 vs. −0.44; \( P = 0.006 \)) and DAS28-CRP (−0.75 vs. −0.41; \( P = 0.010 \)). The difference between new

### Table 2 continued

| Index drug, \( n \) (%) | Total \((N = 448)\) | TNFi cyclers \((N = 239)\) | New MOA switchers \((N = 209)\) | \( P \) value |
|--------------------------|---------------------|---------------------------|-------------------------------|--------------|
| Monotherapy              | 174 (38.8)          | 86 (36.0)                 | 88 (42.1)                     | 0.185        |
| +MTX                     | 169 (37.7)          | 95 (39.7)                 | 74 (35.4)                     | 0.344        |
| +non-MTX csDMARD         | 105 (23.4)          | 58 (24.3)                 | 47 (22.5)                     | 0.657        |
| Prior TNFi               |                     |                           |                               |              |
| Adalimumab SC            | 109 (24.3)          | 54 (22.6)                 | 55 (26.3)                     | 0.360        |
| Certolizumab SC          | 21 (4.7)            | 9 (3.8)                   | 12 (5.7)                      | 0.324        |
| Etanercept SC            | 224 (50.0)          | 152 (63.6)                | 72 (34.5)                     | <0.001       |
| Golimumab IV             | 15 (3.4)            | 5 (2.1)                   | 11 (4.8)                      | 0.114        |
| Golimumab SC             | 1 (0.2)             | 0 (0.0)                   | 1 (0.5)                       | 0.284        |
| Infliximab IV            | 78 (17.4)           | 19 (8.0)                  | 59 (28.2)                     | <0.001       |
| Reason for stopping prior TNFi |                |                           |                               |              |
| Primary ineffectiveness  | 180 (40.2)          | 95 (39.8)                 | 85 (40.7)                     | 0.843        |
| Insurance/cost           | 20 (4.5)            | 14 (5.9)                  | 6 (2.9)                       | 0.127        |
| Secondary loss of efficacy | 92 (20.5)         | 57 (23.9)                 | 35 (16.8)                     | 0.063        |
| Adverse event            | 52 (11.6)           | 20 (8.4)                  | 32 (15.3)                     | 0.022        |
| Patient preference       | 17 (3.8)            | 7 (2.9)                   | 10 (4.8)                      | 0.305        |
| Changed mode/dosage      | 10 (2.2)            | 4 (1.7)                   | 6 (2.9)                       | 0.392        |
| Refill                   | 15 (3.3)            | 7 (2.9)                   | 8 (3.8)                       | 0.598        |
| Othera                   | 22 (4.9)            | 12 (5.0)                  | 10 (4.8)                      | 0.908        |
| Unknown                  | 25 (5.6)            | 12 (5.0)                  | 13 (6.2)                      | 0.581        |

\(\text{ACP A}\) anti-citrullinated protein antibody, \(\text{CDAI}\) Clinical Disease Activity Index, \(\text{csDMARD}\) conventional synthetic disease-modifying antirheumatic drug, \(\text{CRP}\) C-reactive protein, \(\text{DAS28}\) Disease Activity Score, \(\text{ESR}\) erythrocyte sedimentation rate, \(\text{IV}\) intravenous, \(\text{MOA}\) mechanism of action, \(\text{MTX}\) methotrexate, \(\text{RA}\) rheumatoid arthritis, \(\text{RAPID3}\) Routine Assessment of Patient Index Data 3, \(\text{RF}\) rheumatoid factor, \(\text{SC}\) subcutaneous, \(\text{SD}\) standard deviation, \(\text{TNFi}\) tumor necrosis factor inhibitor

\(^a\) Other reasons reported for <2% of patients each were contraindication, surgery, effective, never started, prescription course completed, and no recent visit
MOA switchers and TNFi cyclers for mean change from baseline in RAPID3 score was not statistically significant (−1.45 vs. −1.24; \( P = 0.694 \)).

A post hoc analysis was conducted to examine the relationship between persistence and clinical outcomes with both cohorts combined. Among 366 patients in either cohort with at least 1 year of follow-up, patients who were persistent on either treatment after the switch had significantly greater CDAI reduction from baseline compared with non-persistent patients (−8.69 vs. −3.16; \( P < 0.001 \)) and were significantly more likely to achieve low disease activity or remission, as measured by CDAI <10 (43.1% vs. 24.4%, \( P < 0.001 \)).

**DISCUSSION**

The use of anti-TNF agents has revolutionized rheumatology, yet the patterns of use and rationale for cycling or switching have not been well defined. TNFi cycling may restore clinical benefits after loss of response to the first TNFi [31], and the response to TNFi cycling is greater among patients with secondary loss of efficacy than those with primary lack of response to the initial TNFi [32]. However, fewer than half of patients achieve a significant clinical response after cycling to a second TNFi, and clinical benefits generally become negligible after cycling to a third TNFi [33]. It is important, therefore, to understand whether new MOA switching offers benefits compared with TNFi cycling.

In this study, new MOA switchers were significantly more likely than TNFi cyclers to persist on the study index drug and significantly less likely to switch to another drug after having switched to the study index drug. This analysis did not specify a minimum duration of follow-up post-index, but the median follow-up was approximately 30 months and approximately 85% of patients provided at least 1 year of follow-up data for treatment patterns. In this subgroup, the 1-year persistence rate was
significantly greater in the new MOA switching cohort, and the 1-year switching rate was significantly greater in the TNFi cycling cohort. These results were generally consistent with a previous report that treatment persistence was better for switchers to new MOA therapy (abatacept, rituximab, or tocilizumab) compared with TNFi cyclers [23]. A second study reported that switching to the new MOA therapy tocilizumab or cycling to the TNFi etanercept was associated with better treatment persistence than cycling to adalimumab or infliximab [34]. A third study reported similar treatment persistence rates among patients who cycled to etanercept or switched to the new MOA therapies abatacept or tocilizumab; treatment persistence for other TNFi such as adalimumab or infliximab was not evaluated [17]. A fourth study reported significantly greater treatment persistence after switching to the new MOA DMARDs rituximab or tocilizumab compared with TNFi cycling [35].

Better treatment persistence is associated with better treatment outcomes in RA [36–38], so this analysis also examined clinical outcomes in each cohort. Interventional comparative effectiveness studies are lacking, but observational studies have reported that new MOA switching may be more effective than TNFi cycling. Analyses of 1328 patients in the British Society for Rheumatology Biologics Register [13], the MIRAR study of 1124 patients [14], and the SWITCH-RA study of 728 patients with RA [15] each reported that switching from a TNFi to rituximab was associated with better clinical outcomes than TNFi cycling. A systematic review and Bayesian analysis of published studies determined that switching to a new MOA therapy (abatacept, rituximab, or tocilizumab) was more effective than TNFi cycling in RA patients with an inadequate response to the initial TNFi [39]. Similar results were observed in this study, which expanded upon the previous analyses to include a larger set of new MOA therapies, including abatacept, anakinra,
rituximab, tocilizumab, and tofacitinib. This study also built upon existing literature by examining both treatment persistence and clinical outcomes within the same population.

In the bivariate analysis, compared with TNFi cycling, patients who switched to a new MOA therapy had substantially greater reductions from baseline for CDAI, DAS28-ESR, and DAS28-CRP. Patients who switched to a new MOA therapy also were more likely than TNFi cyclers to achieve a clinically important reduction in CDAI from baseline. However, after adjusting for baseline CDAI, clinical outcomes continued to favor new MOA switchers but the differences from TNFi cyclers were no longer statistically significant. New MOA switchers also had more severe disease activity at baseline, which may have allowed for greater improvement. An advantage of this analysis was the ability to examine the timing of treatment discontinuation with precision, because physicians reported treatment discontinuation prospectively in JointMan instead of being estimated from treatment gaps, which is a standard approach in retrospective claims-based analyses of treatment patterns [40, 41]. JointMan also collected information about the reason for discontinuation of the prior therapy, which cannot be evaluated in claims databases. Significant differences between the cohorts also were observed at baseline for the reported reason for discontinuing the prior TNFi, such as secondary loss of efficacy or adverse events. However, when these reasons were added to the generalized linear model in a post hoc sensitivity analysis, reasons for discontinuation of the prior TNFi did not significantly predict clinical outcomes. In addition, the sample size may have contributed to the inability to detect statistically significant differences in clinical outcomes between the cohorts. A post hoc power analysis based on the actual number of patients that were evaluable for mean change in CDAI showed that the power was <65% to detect a difference of 3 units for CDAI, assuming a common standard deviation of 13.7 and

|                      | TNFi Cyclers | New MOA switchers | P value |
|----------------------|--------------|-------------------|---------|
| **CDAI, mean (SD)**  |              |                   |         |
| Baseline             | 21.70 (12.42) | 24.75 (13.40)     | 0.013   |
| Follow-up            | 16.89 (12.77) | 17.21 (11.82)     | 0.782   |
| Change               | −4.81 (13.82) | −7.54 (13.69)     | 0.037   |
| **DAS28-ESR, mean (SD)** |        |                   |         |
| Baseline             | 3.73 (1.25)  | 4.08 (1.26)       | 0.013   |
| Follow-up            | 3.30 (1.28)  | 3.25 (1.32)       | 0.776   |
| Change               | −0.44 (1.30) | −0.82 (1.25)      | 0.006   |
| **DAS28-CRP, mean (SD)** |        |                   |         |
| Baseline             | 2.99 (1.10)  | 3.26 (1.10)       | 0.030   |
| Follow-up            | 2.58 (1.17)  | 2.51 (1.07)       | 0.558   |
| Change               | −0.41 (1.24) | −0.75 (1.11)      | 0.010   |
| **RAPID3, mean (SD)** |        |                   |         |
| Baseline             | 14.14 (5.63) | 14.97 (5.86)      | 0.131   |
| Follow-up            | 12.90 (5.97) | 13.52 (5.99)      | 0.280   |
| Change               | −1.24 (5.31) | −1.45 (5.90)      | 0.694   |

*CDAI Clinical Disease Activity Index, CRP C-reactive protein, DAS28 Disease Activity Score, ESR erythrocyte sedimentation rate, MOA mechanism of action, RAPID3 Routine Assessment of Patient Index Data 3, SD standard deviation, TNFi tumor necrosis factor inhibitor

a Baseline was the score closest to the study index date between 6 months pre-index and 1 month post-index; end of follow-up was the visit closest to (but not greater than) 12 months post-index

for discontinuation of the prior TNFi did not significantly predict clinical outcomes. In addition, the sample size may have contributed to the inability to detect statistically significant differences in clinical outcomes between the cohorts. A post hoc power analysis based on the actual number of patients that were evaluable for mean change in CDAI showed that the power was <65% to detect a difference of 3 units for CDAI, assuming a common standard deviation of 13.7 and
using a two-group \( t \) test with a 0.05 two-sided significance level.

In this real-world study, more than half of the patients cycled to another TNFi instead of switching from a TNFi to a new MOA. This finding was consistent with several previous studies that reported higher rates of TNFi cycling than new MOA switching in clinical practice [18–25]. Clinicians reported that they were as likely to cycle the patient to another TNFi or switch to a new MOA when the patient had primary ineffectiveness (i.e., they never reached the therapeutic goal with the prior TNFi) and they were significantly more likely to cycle to another TNFi than to switch to a new MOA after secondary loss of efficacy for the prior TNFi. This therapeutic strategy is contrary to evidence from previous studies, which showed that when the reason for stopping the prior TNFi is primary ineffectiveness, a second TNFi is more likely to be ineffective as well [42] and switching to a new MOA is significantly more effective than TNFi cycling in these patients [18]. Thus, there is a need for increased awareness in clinical practice that switching to a new MOA instead of TNFi cycling may be particularly beneficial among patients who stop the prior TNFi because of ineffectiveness. This may be particularly relevant for real-world clinical practice based on the finding that most patients in this study (more than 60%) switched therapy due to either primary or secondary ineffectiveness of the prior TNFi.

Incomplete data entry by providers at some patient encounters may have influenced the analysis. Approximately one in four patients with at least one follow-up visit did not have CDAI reported both at baseline and within 12 months post-index. The number of patients with missing data was greater for DAS28-ESR and DAS28-CRP, which require additional laboratory tests that may not be ordered at every visit. JointMan focuses on the treatment and outcomes of rheumatoid arthritis at rheumatology visits; thus, non-rheumatology conditions (e.g., hypertension, hyperlipidemia) and non-rheumatology medications were not reported consistently in the database and could not be reliably analyzed. Although both academic centers and non-academic practices were represented, the JointMan US clinical database included outpatients treated at participating sites in a limited number of geographic regions that may not reflect the nationwide distribution of locations where RA patients receive treatment. Multivariable analysis adjusted for known patient characteristics that could have influenced treatment persistence or clinical outcomes, but other factors not reported in the JointMan database may have contributed to the study findings. Finally, this analysis was based on broad categories of TNFi or new MOA DMARDs, but individual therapies within the new MOA cohort may have an unequal response. A much larger sample size would be required to detect clinically meaningful differences among individual therapies.

**CONCLUSIONS**

In this real-world analysis of patients with RA who discontinued their prior TNFi, switching to a new MOA DMARD was associated with significantly better treatment persistence than cycling to another TNFi. New MOA switchers also had greater improvement in disease activity...
than TNFi cyclers, but the difference was not statistically significant after adjusting for baseline disease activity. This study suggests that a more evidence-based approach to switching therapy versus cycling is needed in the management of patients with RA.

ACKNOWLEDGEMENTS

Sanofi (Bridgewater, NJ, USA) and Regeneron Pharmaceuticals (Tarrytown, NJ, USA) funded the analyses and the article processing charges. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. Jonathan Latham of PharmaScribe, LLC (on behalf of Sanofi and Regeneron Pharmaceuticals), assisted with the preparation and submission of the manuscript.

Disclosures. Wenhui Wei is an employee of Regeneron Pharmaceuticals and stockholder of Sanofi. At the time of the analysis, Wenhui Wei was an employee of Sanofi. Keith Knapp is an employee and stockholder of Discus Analytics, LLC. Li Wang is an employee of STATinMED Research, which is a paid consultant to Sanofi US. Chieh-I Chen is an employee and stockholder of Regeneron Pharmaceuticals. Gary L. Craig is an employee of Discus Analytics, LLC, and has received fees or honoraria from UCB, Genentech, Celgene, Bristol Myers Squibb, and Premera. Karen Ferguson is an employee of Discus Analytics, LLC, and has received fees or honoraria from Abbvie, Janssen, Pfizer, UCB, Genentech, Novartis, Regeneron, and Sanofi.

Compliance with Ethics Guidelines. No identifiable protected health information was extracted or accessed during the study, pursuant to the US Health Insurance Portability and Accountability Act. Because the study did not involve the collection, use, or transmittal of individually identifiable data, and data were collected in the setting for the usual care of the patient, Institutional Review Board approval to conduct this study was not necessary.

Data Availability. The data sets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheum. 2010;62:1576–82.
2. Birnbaum H, Pike C, Kaufman R, Marynchenko M, Kidolezi Y, Cifaldi M. Societal cost of rheumatoid arthritis patients in the US. Curr Med Res Opin. 2010;26:77–90.
3. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569–81.
4. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008;59:762–84.
5. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64:625–39.
6. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68:1–26.

7. Neovius M, Arkema EV, Olsson H, et al. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis. 2015;74:354–60.

8. Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. Arthritis Res Ther. 2009;11(Suppl 1):S1.

9. Hjardem E, Ostergaard M, Podenphant J, et al. Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor alpha inhibitor? Ann Rheum Dis. 2007;66:1184–9.

10. Hyrich KL, Lunt M, Dixon WG, Watson KD, Symmons DP. Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. Rheumatology (Oxford). 2008;47:1000–5.

11. Lutt JR, Deodhar A. Rheumatoid arthritis: strategies in the management of patients showing an inadequate response to TNFalpha antagonists. Drugs. 2008;68:591–606.

12. Remy A, Avouc J, Gossec L, Combe B. Clinical relevance of switching to a second tumour necrosis factor-alpha inhibitor after discontinuation of a first tumour necrosis factor-alpha inhibitor in rheumatoid arthritis: a systematic literature review and meta-analysis. Clin Exp Rheumatol. 2011;29:96–103.

13. Soliman MM, Hyrich KL, Lunt M, Watson KD, Symmons DP, Ashcroft DM. Rituximab or a second anti-tumor necrosis factor therapy for rheumatoid arthritis patients who have failed their first anti-tumor necrosis factor therapy? Comparative analysis from the British Society for Rheumatology Biologics Register. Arthritis Care Res (Hoboken). 2012;64:1108–15.

14. Gomez-Reino JJ, Maneiro JR, Ruiz J, Rosello R, Sanmarti R, Romero AB. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR Study. Ann Rheum Dis. 2012;71:1861–4.

15. Emery P, Gottenberg JE, Rubbert-Roth A, et al. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. Ann Rheum Dis. 2015;74:979–84.

16. Harold LR, Reed GW, Kremer JM, et al. The comparative effectiveness of abatacept versus anti-tumour necrosis factor switching for rheumatoid arthritis patients previously treated with an anti-tumour necrosis factor. Ann Rheum Dis. 2015;74:430–6.

17. Hirabara S, Takahashi N, Fukaya N, et al. Clinical efficacy of abatacept, tocilizumab, and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies. Clin Rheumatol. 2014;33:1247–54.

18. Finckh A, Ciurea A, Brulhart L, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis. 2010;69:387–93.

19. Kamal KM, Madhavan SS, Hornsby JA, Miller LA, Kavookjian J, Scott V. Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists. Joint Bone Spine. 2006;73:718–24.

20. Reynolds A, Koenig AS, Bananis E, Singh A. When is switching warranted among biologic therapies in rheumatoid arthritis? Expert Rev Pharmacoecon Outcomes Res. 2012;12:319–33.

21. Harnett J, Wiederkem D, Gerber R, Gruben D, Koenig A, Bourret J. Real-world evaluation of TNF-inhibitor utilization in rheumatoid arthritis. J Med Econ. 2016;19:91–102.

22. Baser O, Ganguli A, Roy S, Xie L, Cifaldi M. Impact of switching from an initial tumor necrosis factor inhibitor on health care resource utilization and costs among patients with rheumatoid arthritis. Clin Ther. 2013;35:1454–65.

23. Favalli EG, Biggioggero M, Marcheson A, Mersoni PL. Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies. Rheumatology (Oxford). 2014;53:1664–8.

24. Bergman MJ, Elkin EP, Ogale S, Kamath T, Hamburger MI. Response to biologic disease-modifying anti-rheumatic drugs after discontinuation of anti-tumor necrosis factor alpha agents for rheumatoid arthritis. Rheumatol Ther. 2014;1:21–30.

25. Chatzidionysiou K, van Vollenhoven RF. Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort. Scand J Rheumatol. 2013;42:190–5.

26. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005;7:R796–806.
27. Prevoo ML, van’t Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.

28. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68:954–60.

29. Pincus T, Swearingen CJ, Bergman M, Yazici Y. RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. J Rheumatol. 2008;35:2136–47.

30. Curtis JR, Yang S, Chen L, et al. Determining the minimally important difference in the clinical disease activity index for improvement and worsening in early rheumatoid arthritis patients. Arthritis Care Res (Hoboken). 2015;67:1345–53.

31. Virkki LM, Valleala H, Takakubo Y, et al. Outcomes of switching anti-TNF drugs in rheumatoid arthritis-a study based on observational data from the Finnish Register of Biological Treatment (ROB-FIN). Clin Rheumatol. 2011;30:1447–54.

32. Bombardieri S, Ruiz AA, Fardellone P, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology. 2007;46:1191–9.

33. Navarro-Sarabia F, Ruiz-Montesinos D, Hernandez B, et al. DAS-28-based EULAR response and HAQ improvement in rheumatoid arthritis patients switching between TNF antagonists. BMC Musculoskelet Disord. 2009;10:91.

34. Kobayakawa T, Kojima T, Takahashi N, et al. Drug retention rates of second biologic agents after switching from tumor necrosis factor inhibitors for rheumatoid arthritis in Japanese patients on low-dose methotrexate or without methotrexate. Mod Rheumatol. 2015;25:251–6.

35. Rotar Z, Hočevar A, Rebolj Kodre A, Praprotnik S, Tomšič M. Retention of the second-line biologic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis failing one tumor necrosis factor alpha inhibitor: data from the BioRx.ssi registry. Clin Rheumatol. 2015;34:1787–93.

36. Contreras-Yáñez I, Pascual-Ramos V. Window of opportunity to achieve major outcomes in early rheumatoid arthritis patients: how persistence with therapy matters. Arthritis Res Ther. 2015;17:177.

37. Pascual-Ramos V, Contreras-Yáñez I, Villa AR, Cabeldes J, Rull-Gabaret M. Medication persistence over 2 years of follow-up in a cohort of early rheumatoid arthritis patients: associated factors and relationship with disease activity and with disability. Arthritis Res Ther. 2009;11:R26.

38. Pasma A, Schenk CV, Timman R, et al. Non-adherence to disease-modifying antirheumatic drugs is associated with higher disease activity in early arthritis patients in the first year of the disease. Arthritis Res Ther. 2015;17:281.

39. Kim HL, Lee MY, Park SY, et al. Comparative effectiveness of cycling of tumor necrosis factor-alpha (TNF-alpha) inhibitors versus switching to non-TNF biologics in rheumatoid arthritis patients with inadequate response to TNF-alpha inhibitor using a Bayesian approach. Arch Pharm Res. 2014;37:662–70.

40. Bonafede MM, Curtis JR, McMorrow D, Mahajan P, Chen CI. Treatment effectiveness and treatment patterns among rheumatoid arthritis patients after switching from a tumor necrosis factor inhibitor to another medication. Clinicoecon Outcomes Res. 2016;8:707–15.

41. Chastek B, Becker LK, Chen CI, Mahajan P, Curtis JR. Outcomes of tumor necrosis factor inhibitor cycling versus switching to a disease-modifying anti-rheumatic drug with a new mechanism of action among patients with rheumatoid arthritis. J Med Econ 2017;20:1–10.

42. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum. 2007;56:13–20.

43. Discus Analytics LLC. The JointMan® Product Suite Portfolio. http://t3jointman.com/wp-content/uploads/2015/12/JM-Marketing-Booklet-Pages.pdf. Accessed 14 June 2017