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ORIGINAL ARTICLE

Persistence With Conventional Triple Therapy Versus a Tumor Necrosis Factor Inhibitor and Methotrexate in US Veterans With Rheumatoid Arthritis

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Objective. **To compare persistence and adherence to triple therapy with the nonbiologic disease-modifying antirheumatic drugs (DMARDs) methotrexate (MTX), hydroxychloroquine, and sulfasalazine, versus a tumor necrosis factor inhibitor (TNFi) plus MTX in patients with rheumatoid arthritis (RA).**

Methods. **Administrative and laboratory data were analyzed for US Veterans with RA initiating triple therapy or TNFi + MTX between January 2006 and December 2012. Treatment persistence 365 days postindex was calculated using 3 definitions. Definition 1 required no gap in therapy of ≥90 days for any drug in the original combination. Definition 2 required no added or switched DMARD, no decrease to nonbiologic DMARD monotherapy, and no termination of all DMARD therapies. Definition 3 was similar to definition 2 but allowed a switch to another drug within the same class. Adherence used a proportion of days covered of ≥80%. Propensity-weighted analysis with matched weights was used to balance covariates.**

Results. **The analysis included 4,364 RA patients (TNFi + MTX, n = 3,204; triple therapy, n = 1,160). In propensity-weighted analysis, patients in the TNFi + MTX group were significantly more likely than patients in the triple therapy group to satisfy all persistence criteria in definition 1 (risk difference [RD] 13.1% [95% confidence interval (95% CI) 9.2–17.0]), definition 2 (RD 6.4% [95% CI 2.3–10.5]), and definition 3 (RD 9.5% [95% CI 5.5–13.6]). Patients in the TNFi + MTX group also exhibited higher adherence during the first year (RD 7.2% [95% CI 3.8–10.5]).**

Conclusion. **US Veterans with RA were significantly more likely to be persistent and adherent to combination therapy with TNFi + MTX than triple therapy with nonbiologic DMARDs.**

INTRODUCTION

Research estimates that 1.3–1.5 million adults in the US have rheumatoid arthritis (RA) (1,2). The American College of Rheumatology guidelines for use of disease-modifying antirheumatic drugs (DMARDs) and biologic agents in the treatment of RA (3,4) recommend nonbiologic DMARD therapy alone, combination nonbiologic DMARD therapy (double or triple therapy), or biologic agents, including tumor necrosis factor inhibitors (TNFi), with or without methotrexate (MTX) or other DMARDs. The recommendations include tailoring treatment based on disease duration and disease activity (3–6).

Three prospective clinical trials compared triple therapy (MTX + hydroxychloroquine + sulfasalazine) to a TNFi +

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Significance & Innovations

- Veterans who initiated combination therapy with a tumor necrosis factor inhibitor and methotrexate (TNFi + MTX) showed a higher proportion of persistence at 1 year compared with Veterans who initiated triple therapy.
- Veterans who initiated TNFi + MTX combination therapy showed a higher proportion of adherence at 1 year compared with Veterans who initiated triple therapy.
- The lower adherence and persistence in the triple therapy group may be due to the increased regimen complexity of multiday dosing.
- Methods to improve adherence and persistence are needed for both treatment groups.

MTX combination in patients with RA (7–9). One reported that a TNFi + MTX combination was clinically superior to triple therapy at 1 year (7), while the others showed similar clinical efficacy between the treatment arms (8,9). Patients in all 3 trials had good-to-excellent treatment adherence. The nonblinded trial reported that 82% of patients who added a TNFi to MTX and 68% of patients who received triple therapy continued using their assigned therapy at 12 months (7); at 24 months, adherence rates were 70% and 57%, respectively (10). The other trials reported nondifferential adherence between treatment arms in patients remaining on protocol: 1 reported patients had good or excellent adherence at 94% of visits through 2 years of followup (8), and the other reported 78–79% of patients were adherent through 48 weeks of followup (9). However, these rates did not include patients who withdrew from the trials.

By contrast, a recent analysis of US commercially insured beneficiaries with RA found that less than one-third of patients were persistent or adherent to triple therapy or etanercept-MTX combination therapy, and triple therapy users had significantly lower odds of being persistent or adherent than users of 2-drug biologic combination therapy (11). Discrepancies between trials and real-world analyses may signal unrealized treatment benefits from nonpersistence and nonadherence. This analysis assessed US Veterans to explore persistence and adherence in a noncommercial health care system. The objective of this study was to compare persistence and adherence during the first year after initiation of triple therapy versus initiation of TNFi + MTX combinations in US Veterans with RA.

PATIENTS AND METHODS

Study design. This open cohort study used administrative and clinical databases with national data from the Department of Veterans Affairs (VA), Veterans Health Administration (VHA), Corporate Data Warehouse, Pharmacy Benefits Management, and Decision Support Services (12–14). The research was conducted in compliance with the Helsinki Declaration, approved by the Institution Review Board of the University of Utah (IRB_00012917), and reviewed by the Salt Lake City VA Research Review Committee.

This study included VA patients who initiated TNFi + MTX combination therapy or triple therapy (sulfasalazine, hydroxychloroquine, and MTX) between January 2006 and December 2012. TNFi drugs included adalimumab, certolizumab, etanercept, golimumab, and infliximab. Patients were ages ≥18 years and had observations recorded ≥182 days before and ≥365 days after starting combination therapy, with ≥1 health care encounter within 365 days after initiating therapy, to ensure that they were still actively using the VHA system. They were also required to have a diagnosis of RA (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 714.0) within 182 days preindex or 28 days postindex.

Patients were excluded if they had a diagnosis (ICD-9-CM) of juvenile idiopathic arthritis (714.3x), psoriasis (696.1x), psoriatic arthritis (696.0x), ankylosing spondylitis (720.0x), Crohn's disease (555.xx), or ulcerative colitis (556.xx) in the baseline period, as some nonbiologic and/or biologic DMARDs are indicated for the treatment of these conditions. Patients could not have J-codes for intravenous administration of MTX (J8610, J9250, and J9260) during the postindex period, which would suggest treatment for cancer.

Candidates for the triple therapy group had dispensing for all 3 medications (hydroxychloroquine, sulfasalazine, and MTX) that overlapped by ≥1 day. Candidates for the combination TNFi + MTX group had a dispensing or administration for a TNFi and MTX that overlapped by ≥1 day. The index date (day 1) was the date the last drug (index drug) required to complete the combination was dispensed or administered. To ensure the index drug was intended to be part of combination therapy, all other drugs (foundation drugs) in the triple therapy combination or TNFi + MTX combination were required to have 1 additional prescription refill/administration within 90 days after initiation of the newest index drug. This method ensured that the provider and patient intended to use combination therapy and were not just switching between DMARDs with an overlap. Supplementary Figure 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22944/abstract) illustrates the approach taken to identify patients who received triple therapy or TNFi + MTX combination therapy.

Patients with prescriptions for all combination drugs on the index date (both drugs in the TNFi + MTX group and all 3 drugs in the triple therapy group) were excluded if they had received each drug in the combination at least once during the preindex period (182 days before the index date). Patients in the TNFi + MTX group could not have a nonfoundation or nonindex biologic DMARD (TNFi or other) during the preindex period. Patients in either treatment group could not receive any nonbiologic DMARDs other than index or foundation between 30 days before and day 28. No other DMARDs beyond combination DMARDs (triple therapy and TNFi + MTX) could be available on the index date.

Persistence. Determination of persistence and adherence was based on days supply from the pharmacy outpatient package. Previous algorithms were developed to validate and correct quantity and days supply (15–17). Corrected

Table 1. Sample attrition*

	No. removed	No. remaining
Received combination therapy between 2006 and 2012	–	14,272
Refilled foundation drug(s)	1,179	13,093
≥365 followup days and ≥182 preindex days	789	12,304
Age >18 years	0	12,304
RA diagnosis†	3,402	8,902
Exclude PsO, PsA, AS, UC, CD, JIA diagnosis†	567	8,335
Exclude MTX J-code	56	8,279
Exclude index drug during preindex period	1,038	7,241
≥1 drug had no prescription in preindex period	1,075	6,166
Exclude noneligible biologic DMARD in preindex period	202	5,964
Exclude noneligible nonbiologic DMARD‡	1,551	4,413
Exclude noneligible DMARD on index date	49	4,364

* RA = rheumatoid arthritis; PsO = psoriasis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; UC = ulcerative colitis; CD = Crohn's disease; JIA = juvenile idiopathic arthritis; MTX = methotrexate; DMARD = disease-modifying antirheumatic drug.
† Between 182 days before and day 28.
‡ Between 30 days before and day 28.

days supply was used for all outpatient-dispensed medications. The days supply for infliximab was assumed to be 56 days unless there was evidence of an infliximab infusion before then.

Persistence was analyzed with 3 definitions. Definition 1 was the primary outcome measure and represented complete persistence in taking both TNFi combination or all 3 triple therapy combination therapy drugs; definition 2 allowed dropping 1 nonbiologic DMARD, and definition 3 allowed dropping 1 nonbiologic DMARD or changing medications within a class.

Persistence definition 1 required a patient to continue all drugs in the combination without a ≥90-day gap in therapy. A patient was considered nonpersistent if there was a gap of ≥90 days for any drug in the combination beyond the last day of a prescribed dispensing period. Patients who added another DMARD were considered persistent in the primary analysis if other drugs were continued without a gap in therapy. The date of nonpersistence was defined as the day immediately before the first gap of ≥90 days started for any treatment in the combination at the end of days supply or usual infusion dosing interval.

For persistence definition 2, patients were considered nonpersistent 1) if a new DMARD (biologic or nonbiologic) was started, either because of a switch in therapy or because the drug was added to the combination, 2) if, after a ≥90-day gap in therapy, the patient received only nonbiologic DMARD monotherapy (i.e., the patient stopped 2 of 3 drugs in the triple combination or stopped TNFi in the TNFi + MTX combination), or 3) if the entire combination therapy was terminated. The date of nonpersistence was the earliest date on which the treatment was switched, added, or reduced to nonbiologic monotherapy or no therapy.

For persistence definition 3, patients were considered nonpersistent in the same manner as definition 2, but they were allowed to switch drugs within a class. Specifically, patients were considered nonpersistent 1) if a DMARD of another class was started, 2) if, after a ≥90-day gap in therapy, the patient received only nonbiologic DMARD monotherapy, or 3) if the entire combination therapy was terminated. The date of nonpersistence was the earliest date on which the treatment was switched to a DMARD of another class or was reduced to nonbiologic monotherapy or no therapy.

Adherence. The proportion of days covered (PDC) was used to measure adherence (18). Patients with PDC ≥80% for each medication in the combination were considered adherent. For both persistence and adherence measures, patients were assumed not to be doubling up on medication when early refill occurred. An overlapping dispensing period because of early refill was shifted to a later time period (right shift) as if patients were continuously using the drug, but it was not used to fill gaps between previously dispensed episodes before overlapping days (left shift). The maximum allowed right shift for early refill was 14 days.

Covariates. Clinically plausible confounders of the relationship between initiating triple therapy or TNFi + MTX therapy were extracted from VHA data and used as baseline covariates. The baseline period was 1 year preindex for combination therapy for all diagnoses, medications, and utilization variables. Proportions of patients with positive rheumatoid factor (RF) or cyclic citrullinated peptide (CCP) antibody were based on patients with evaluable data. The Healthcare Cost and Utilization Project Clinical Classification System (HCUP CCS) for ICD-9-CM conditions was used to identify specific medical conditions. The HCUP CCS was also used for an overall measure of comorbidity by counting the unique number of single-level conditions each patient experienced during the baseline year. Additional aggregate measures included the distinct count of VA Drug Class codes and the Rheumatic Disease Comorbidity Index (RDCI) score (19). Aggregate measures of health care utilization in the baseline period included yearly counts of rheumatology visits (stop code 314), urgent care visits (stop code 131), emergency department visits (stop code 130), and inpatient visits (admission counts). VA Drug Class codes were used to identify opioid analgesics (CN101), nonopioid analgesics (CN103), salicylates, antirheumatics (MS101), nonsalicylate nonsteroidal antiinflammatory drugs (MS102), and prednisone (HS051). Proton pump inhibitors were identified by string search on generic ingredients.

Statistical analysis. Propensity score analysis used matching weights to adjust for baseline patient characteristics and balance the 2 combination therapy groups (20,21). The matched-weight approach is theoretically equivalent to the 1:1 exact-matching propensity score, which focuses on the subset of patients who have common support, meaning there is an expectation about clinical equipoise between the 2 treatment choices. The matched-weight approach has proven to be more efficient and has better statistical properties than the 1:1 matching approach (20). Thirty-four pretreatment baseline covariates were identified as possible confounders based on literature review and the assumption

Table 2. Propensity score analysis for unadjusted and adjusted covariates measured in the year before the start of followup*

Method	Unadjusted			Matched weights adjusted		
	TNFi + MTX	Triple therapy	Standard difference	TNFi + MTX	Triple therapy	Standard difference
No. of patients	3,204	1,160	–	1,143.2	1,136.1	–
Demographics						
Age, mean ± SD years	61.2 ± 10.8	62.2 ± 9.8	0.098†	62.2 ± 6.1	62.2 ± 9.7	0.001
Body mass index, mean ± SD kg/m^2	29.4 ± 6.3	29.7 ± 8.0	0.038	29.7 ± 3.7	29.7 ± 7.9	0.001
Male	2,775 (86.6)	1,053 (90.8)	0.132‡	1,035.9 (90.6)	1,029.5 (90.6)	< 0.001
VA drug class						
Distinct classes, mean ± SD	9.3 ± 4.9	11.2 ± 5.2	0.373‡	11.1 ± 3.3	11.0 ± 4.8	0.038
Opioid analgesics	1,269 (39.6)	479 (41.3)	0.034	468.5 (41.0)	462.3 (40.7)	0.006
Nonopioid analgesics	733 (22.9)	364 (31.4)	0.192‡	351.8 (30.8)	345.7 (30.4)	0.007
Salicylates, antirheumatic	62 (1.9)	34 (2.9)	0.065§	31.4 (2.7)	31.2 (2.7)	< 0.001
Prescription NSAID	1,220 (38.1)	500 (43.1)	0.103†	495.9 (43.4)	491.6 (43.3)	0.002
Proton pump inhibitor	1,272 (39.7)	559 (48.2)	0.172‡	555.5 (48.6)	542.3 (47.7)	0.017
Any prednisone	1,559 (48.7)	649 (56.0)	0.146‡	642.8 (56.2)	629.3 (55.4)	0.017
CCS comorbidity						
Distinct count, mean ± SD	9.6 ± 5.9	10.6 ± 6.9	0.157‡	10.3 ± 3.9	10.3 ± 6.5	0.012
Tuberculosis	22 (0.7)	3 (0.3)	0.062	3.0 (0.3)	3.0 (0.3)	< 0.001
CHF, nonhypertensive	56 (1.7)	55 (4.7)	0.170‡	40.8 (3.6)	41.2 (3.6)	0.003
Pneumonia	31 (1.0)	21 (1.8)	0.072§	15.4 (1.3)	15.3 (1.3)	< 0.001
Acute bronchitis	47 (1.5)	18 (1.6)	0.007	16.1 (1.4)	16.4 (1.4)	0.003
Urinary tract infection	56 (1.7)	12 (1.0)	0.061	11.7 (1.0)	11.6 (1.0)	0.001
Skin infection	81 (2.5)	37 (3.2)	0.040	36.4 (3.2)	34.8 (3.1)	0.007
Septicemia	3 (0.1)	6 (0.5)	0.077†	2.5 (0.2)	2.2 (0.2)	0.006
Shock	1 (0.0)	1 (0.1)	0.023	1.0 (0.1)	1.0 (0.1)	< 0.001
HIV infection	3 (0.1)	1 (0.1)	0.003	1.0 (0.1)	1.0 (0.1)	0.001
Hepatitis	39 (1.2)	15 (1.3)	0.007	15.7 (1.4)	14.9 (1.3)	0.006
Alcohol-related disorders	89 (2.8)	62 (5.3)	0.13‡	54.4 (4.8)	54.2 (4.8)	0.001
Substance-related disorders	61 (1.9)	32 (2.8)	0.057	29.5 (2.6)	28.8 (2.5)	0.003
RDCI score, mean ± SD	1.6 ± 1.5	1.8 ± 1.6	0.130‡	1.8 ± 0.9	1.8 ± 1.6	0.009
CCP antibody test and result						
Any CCP antibody test	2,375 (74.1)	940 (81.0)	0.166‡	866.5 (75.8)	920.8 (81.1)	0.128
CCP antibody positive	1,774 (55.4)	682 (58.8)	0.069§	613.5 (70.8)	670.6 (72.8)	0.045
Rheumatoid factor test and result						
Any rheumatoid factor test	2,908 (90.8)	1,079 (93.0)	0.083§	1,042.8 (91.2)	1,057.5 (93.1)	0.069
Rheumatoid factor positive	1,995 (62.3)	772 (66.6)	0.090†	740.8 (71.0)	755.2 (71.4)	0.008
Smoking						
Smoking status reported	2,933 (91.5)	1,082 (93.3)	0.066	1,056.9 (92.5)	1,058.9 (93.2)	0.029
Ever smoked	2,048 (63.9)	793 (68.4)	0.094†	770.3 (72.9)	776.0 (73.3)	0.009
No. of visits, mean ± SD						
Emergency department	0.0 ± 0.2	0.0 ± 0.3	0.050	0.0 ± 0.2	0.0 ± 0.3	0.004
Rheumatology	2.5 ± 1.8	2.6 ± 1.7	0.096†	2.6 ± 1.1	2.6 ± 1.7	0.014
Urgent care	0.0 ± 0.1	0.0 ± 0.1	0.044	0.0 ± 0.1	0.0 ± 0.1	0.008
Inpatient	0.1 ± 0.4	0.2 ± 0.6	0.164‡	0.1 ± 0.3	0.1 ± 0.5	0.009

* Values are the number (%) unless indicated otherwise. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate; VA = Veterans Affairs; NSAID = nonsteroidal antiinflammatory drug; CCS = Clinical Classification System; CHF = congestive heart failure; HIV = human immunodeficiency virus; RDCI = rheumatic disease comorbidity index; CCP = cyclic citrullinated peptide.
† $P < 0.01$.
‡ $P < 0.001$.
§ $P < 0.05$.

that these variables might influence treatment decisions and persistence at 1 year of followup. Covariates were then used to generate a propensity score (e_i) using potential confounders (X) to model treatment choice (Z) for each patient using a logistic regression model:

$$e_i = e(\mathbf{X}_i) = \Pr(Z_i = 1 | \mathbf{X}_i)$$

The matching weight for patient i (W_i) was a variant of inverse probability weight (22) with $\min(1-e_i, e_i)$ in the numerator:

$$W_i = \frac{\min(1-e_i, e_i)}{Z_i e_i + (1-Z_i)(1-e_i)}$$

The matching-weight estimator of the treated effect was calculated as follows, which can be interpreted as the difference in weighted risks between treatment groups:

$$\hat{\Delta}_{MW} = \frac{\sum_{i=1}^{n} W_i Z_i Y_i}{\sum_{i=1}^{n} W_i Z_i} - \frac{\sum_{i=1}^{n} W_i (1-Z_i) Y_i}{\sum_{i=1}^{n} W_i (1-Z_i)}$$

Figure 1. Propensity score analysis with standardized difference scores before and after application of matched weights. VA = Veterans Affairs; NSAID = nonsteroidal antiinflammatory drug; CCS = Clinical Classification System; HIV = human immunodeficiency virus; RDCI = rheumatic disease comorbidity index; CCP = cyclic citrullinated peptide; ED = emergency department.

Relative differences on the ratio scale were also reported. Variance was computed using the sandwich variance estimator (20).

The ability to check covariate balance between treatment groups is an advantage of propensity score methods over direct regression. Lack of balance often suggests that treatment comparison may not be feasible in certain subgroups of patients without extrapolation or that there may be residual bias due to confounding by covariates (23). Standardized differences were used to determine differences in covariate balance before and after weighting:

$$\frac{100\times(\bar{x}_{(1)}-\bar{x}_{(0)})}{\sqrt{(s^2_{(1)}+s^2_{(0)})/2}}$$

This formula can be computed using weighted means and variances. In typical applications of pair-matching methods, standardized differences in a good match are a few percentage points. As a threshold for claiming balance, 10% has been advocated (23). Standardized differences using matching-weights methods can easily reach below 1%. Therefore, the matching-weights method may lead to a substantially better covariate balance than the pair-matching method (20). Matched weights–adjusted Kaplan-Meier plots were created to illustrate persistence among treatment groups. Microsoft SQL server and SAS, version 9.4, with Enterprise Guide, version 6.1, were used to prepare data and conduct statistical analyses.

RESULTS

Patient characteristics. Of 14,272 patients who received either combination therapy regimen during the study period, 4,364 met all inclusion and exclusion criteria (Table 1), including 3,204 who initiated TNFi + MTX and 1,160 who initiated triple therapy. Compared with patients who initiated TNFi + MTX, patients who initiated triple therapy were older (mean age 62.2 versus 61.2 years), more likely to be men (90.8% versus 86.6%), and more likely to have concurrent illness based on concomitant medications, comorbid conditions, RDCI scores, CCP antibody and RF positivity, smoking history, and health care visits (Table 2). Propensity score analysis using matched weights was used to balance covariates (Figure 1).

Persistence results. Crude analyses and those using a matched weights–adjusted model for each definition of persistence are summarized in Table 3. In each propensity-weighted analysis, persistence was significantly higher for patients who initiated TNFi + MTX versus patients who initiated triple therapy. The absolute risk difference (RD) of persistence was 13.1% (95% confidence interval [95% CI] 9.2–17.0) for definition 1 (Figure 2), 6.4% (95% CI 2.3–10.5) for definition 2 (Figure 3), and 9.5% (95% CI 5.5–13.6) for definition 3 (Figure 4). Kaplan-Meier plots for the propensity-matched population by persistence definition consistently showed that persistence with triple therapy was significantly lower than with combination TNFi therapy.

Adherence results. A higher proportion of patients in the TNFi + MTX group was considered adherent with all therapies at 1 year versus the triple therapy group (Table 3). The proportion of adherent patients (PDC ≥80%) was 24.2% for TNFi + MTX and 17.3% for triple therapy ($P < 0.001$) in the unadjusted model and 24.5% and 17.3%, respectively, in the adjusted model. The RD for adherence was 6.9% (95% CI 4.2–9.5) in the unadjusted model and 7.2% (95% CI 3.8–10.5) in the adjusted model.

Unadjusted PDCs for individual agents in the TNFi + MTX combination were 48.0% for TNFi and 40.4% for MTX (Table 4). Unadjusted PDCs for individual agents in the triple therapy combination were 29.8% for sulfasalazine, 48.6% for MTX, and 48.0% for hydroxychloroquine.

DISCUSSION

Lower persistence and adherence represent deficient drug utilization and are often correlated with a greater extent of unrealized treatment benefit and poorer clinical outcomes in RA (24–27). In this analysis of claims data for 4,364 US

Table 3. Persistence and adherence for crude and adjusted rates at 1 year*

Outcome	TNFi + MTX	Triple therapy	Relative risk (95% CI)	Risk difference, % (95% CI)
Crude model†				
Persistence				
Definition 1	1,361 (42.5)	339 (29.2)	1.45 (1.32–1.60)	13.3 (10.1–16.4)
Definition 2	1,765 (55.1)	550 (47.4)	1.16 (1.09–1.24)	7.7 (4.3–11.0)
Definition 3	1,937 (60.5)	577 (49.7)	1.22 (1.14–1.30)	10.7 (7.4–14.1)
Adherence	775 (24.2)	201 (17.3)	1.40 (1.21–1.61)	6.9 (4.2–9.5)
Adjusted model‡				
Persistence				
Definition 1	483.66 (42.3)	331.86 (29.2)	1.45 (1.29–1.62)	13.1 (9.2–17.0)
Definition 2	613.54 (53.7)	536.88 (47.3)	1.14 (1.05–1.23)	6.4 (2.3–10.5)
Definition 3	676.31 (59.2)	563.88 (49.6)	1.19 (1.10–1.29)	9.5 (5.5–13.6)
Adherence	279.96 (24.5)	196.98 (17.3)	1.41 (1.20–1.66)	7.2 (3.8–10.5)

* Values are the number (%) unless indicated otherwise. Definition 1 was no gap in therapy of ≥90 days for any drug in the original combination. Definition 2 was no added or switched disease-modifying antirheumatic drug (DMARD), no decrease to nonbiologic DMARD monotherapy, and no termination of all DMARD therapies. Definition 3 was similar to definition 2 but allowed a switch to another drug within the same class. Adherence was proportion of days covered of ≥80% for each medication in the combination. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate; 95% CI = 95% confidence interval.
† TNFi + MTX: n = 3,204; triple therapy: n = 1,160.
‡ TNFi + MTX: n = 1,143.2; triple therapy: n = 1,136.1.

veteran patients with RA, initiation of the TNFi + MTX combination was associated with significantly greater treatment persistence in the first year compared with initiation of triple therapy with 3 nonbiologic DMARDs. An observational study of commercially insured patients also showed higher persistence with TNFi + MTX than with triple therapy (11). These findings are consistent with those in 1 open-label clinical trial (7) but differ from those in 2 blinded clinical trials that showed very similar outcomes in persistence between patients taking TNFi + MTX and those using triple therapy (8,9). Clinical trials typically try to identify treatment effects that represent the highest internal validity possible. Thus, it is often necessary to ensure that medication usage is tightly controlled and protocol based, leading to high, undifferentiated medication persistence and adherence in all treatment arms. As shown in this study, ideal medication usage environments in clinical trials may overestimate persistence and adherence in the real world where patients and/or physicians may alter therapy use on an as-needed basis, and there is less patient selection (as in a trial) of patients more likely than not to adhere to the study protocol.

Three methods for defining persistence were used in this analysis to explore the sensitivity of various approaches that used different clinical assumptions. The primary analysis was a direct assessment of persistence without any clinical assumptions; this approach required a patient to continue all drugs in the combination for ≥365 days without any gap in therapy that was of ≥90 days. To explore the potential that patients who were doing well may have discontinued 1 nonbiologic DMARD of the combination, 2 alternative definitions of persistence were used. Persistence definition 2 incorporated the concept of clinical effectiveness into the

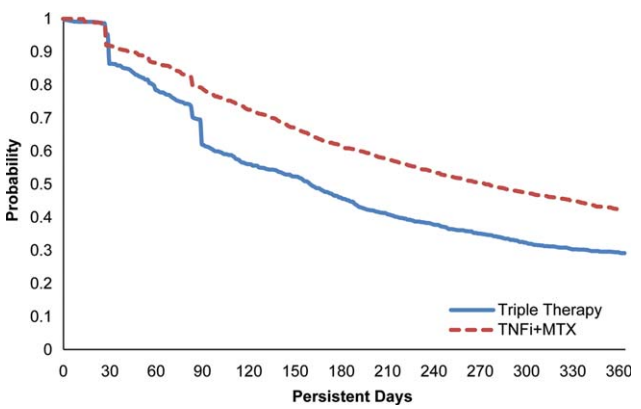

Figure 2. Kaplan-Meier plot for persistence with matching weights, definition 1: no gap in therapy of ≥90 days for any drug in the original combination. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/doi/10.1002/acr.22944/abstract.

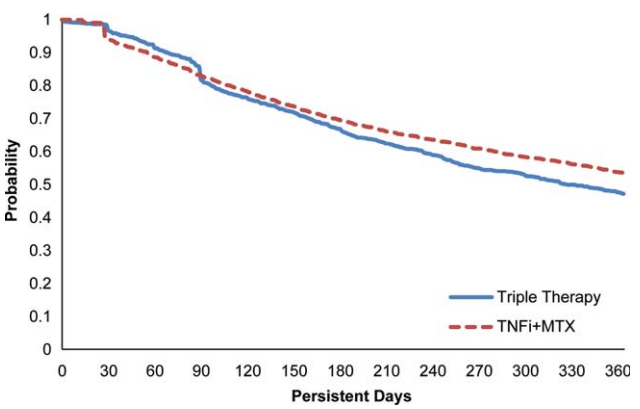

Figure 3. Kaplan-Meier plot for persistence with matching weights, definition 2: no added or switched disease-modifying antirheumatic drug (DMARD), no decrease to nonbiologic DMARD monotherapy, and no termination of all DMARD therapies. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/doi/10.1002/acr.22944/abstract.

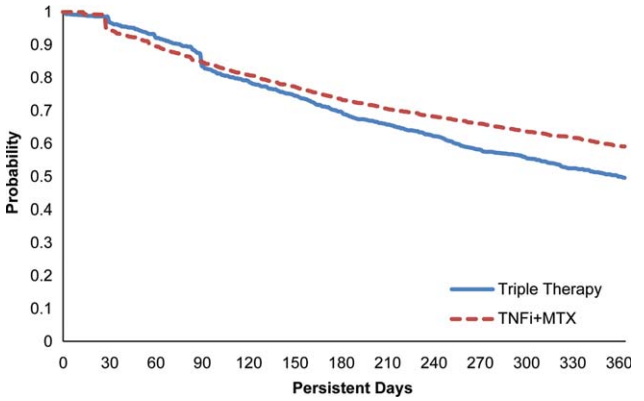

Figure 4. Kaplan-Meier plot for persistence with matching weights, definition 3: similar to definition 2, but allowed a switch to another drug within the same class. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/doi/10.1002/acr.22944/abstract.

analysis of persistence by allowing patients to reduce the use of nonbiologic DMARDs. In clinical practice, patients who respond to combination therapy and have low disease activity may interrupt or stop 1 or more nonbiologic DMARDs in the combination. Persistence definition 3 explored potential explanations for differences in persistence by allowing patients to be persistent during 1-year followup, even if they switched drugs within a class, as long as they did not discontinue to nonbiologic DMARD monotherapy or to no DMARD therapy. The additional assumption was that drugs in the same class would have similar effectiveness, and thus, switching between them would be no different from persistence with the original drug. With these definitions of persistence, rates were higher in both treatment groups than for the primary method and continued to be statistically significantly higher for TNFi + MTX than for triple therapy, as seen with the primary method.

Adherence rates were also significantly higher for TNFi + MTX than for triple therapy. Adherence analysis of individual treatments found lower adherence to sulfasalazine (30%) compared with all other DMARDs (≥40%). One explanation that cannot be confirmed by this study is that once or twice daily therapy with hydroxychloroquine and sulfasalazine, which can require up to 6 tablets per day in divided doses, may be associated with lower persistence and adherence than drug schedules that require MTX injection once weekly and TNFi administration once weekly or less frequently. The observation that sulfasalazine adherence was much less than that for other agents supports this concept but is not conclusive. Previous reports show decreased adherence with multiple daily dosing of sulfasalazine for inflammatory bowel disease (28) and a general decrease in adherence with frequent medication dosing (29,30). A lack of adherence may be associated with a lack of efficacy that could lead to termination of combination therapy. Provider and patient perceptions could also lead to differential adherence with different combination therapies.

The greatest 1-day drops in persistence with the initiated combination were at 30 days and 90 days postindex. The clinical reason could not be fully determined but suggests that many patients did not refill their index drug after the first 30-day or 90-day prescription. In an additional analysis (not presented here), we evaluated persistence to therapy in each group among patients who were persistent for >100 days to determine whether observed differences were due to initial drops at 30 and 90 days. Persistence patterns were similar to those in the primary report, with a higher level of persistence in patients who initiated TNFi + MTX in comparison with triple therapy, suggesting that an early drop after a single index drug refill could not fully explain the difference in the observed persistence.

Overall, persistence and adherence were low, but these findings are consistent with other analyses conducted in the VA and commercial settings. In a previous study, we found overall adherence for TNFi during the index year to be 50% in RA patients (17). Adherence by TNFi agent ranged from 41% to 50%. Low persistence was also found in a commercial study comparing persistence between etanercept-MTX and triple therapy initiators (11). At 1 year, only 28% of the etanercept-MTX group remained persistent, while 18% of the triple therapy group remained persistent. In our study, persistence rates were dependent on the definition but reflected previously published expectations about persistence and adherence during the index year.

Nonadherence and nonpersistence could result in reduced clinical benefit with these therapies. We previously reported our experience using observational data in US Veterans to demonstrate that higher adherence with MTX is associated with improved clinical outcomes, as measured by mean disease activity scores over followup (27). We did not have clinical outcome measures to determine whether differences in adherence were associated with reduced clinical benefit; however, our prior report supports this expectation. Conversely, without clinical outcomes data, we could not determine whether differences in treatment effectiveness or tolerability led to observed differences in adherence and persistence in this analysis, but registry studies have reported that ineffectiveness and adverse events are the leading reasons for treatment discontinuation in RA (31–34). Many other factors associated with medication adherence (35–47) were not addressed in this analysis, but there is no reason to

Table 4. Unadjusted 1-year adherence rate (≥80% proportion of days covered) by individual agent*

Treatment group	Agent	Adherent patients	*P*
TNFi + MTX (n = 3,204)	Both†	775 (24.2)	–
	TNFi	1,538 (48.0)	–
	MTX	1,295 (40.4)	–
Triple therapy (n = 1,160)	All†	201 (17.3)	< 0.001‡
	Sulfasalazine	346 (29.8)	–
	MTX	564 (48.6)	–
	Hydroxychloroquine	557 (48.0)	–

* Values are the number (%) unless indicated otherwise. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate.
† Proportion of days covered in the first year was ≥80% for both/all drugs in the combination.
‡ Between the TNFi + MTX and triple therapy groups.

suspect that these differences were unevenly distributed in this population between the TNFi + MTX and triple therapy groups. Strategies to improve adherence, particularly during initial treatment phases (e.g., at the first expected refill), possibly could lead to improved clinical outcomes that motivate patients to continue combination therapy.

This study has the strengths of a large population of Veterans across the US as well as a uniform system to capture pharmacy data, which allowed for comparison among these patients from different sites. This study also had several potential limitations. A diagnosis of RA was identified using ICD-9-CM diagnosis codes, which are subject to potential miscoding. We could only determine whether patients obtained DMARDs, not whether they actually took DMARDs as prescribed. As this study was a retrospective cohort study, results may not have indicated any causal relationships between exposure and outcomes (48). The study of US Veterans who are predominantly male, older, and with more comorbid conditions than a general RA population may not be generalizable to other patient populations. However, a separate study in a commercially insured population reported results similar to this study (11). The primary analysis provided the most direct assessment of whether a patient persisted with the original combination during the first year of followup, but it did not provide any information about reasons for nonpersistence. Although persistence definitions 2 and 3 were designed to include patients in persistence rates if their changes in therapy were consistent with effective treatment, these changes may also have reflected loss of efficacy, safety issues, drug costs, or patient or provider preferences that could not be assessed in this analysis. Other unmeasured confounders may have affected the association identified between treatment regimen and treatment patterns. Patients who initiated triple therapy had more comorbidities than patients who initiated TNFi + MTX based on baseline covariates, but these differences did not appear to confound the relationship between treatment groups and outcomes, because results in the weighted analysis were similar to crude results. The results of this study are intended to describe, not to influence, current clinical practice.

Given that both outcomes and exposure were defined using pharmacy dispensing and administration data, there was an inherent risk of information bias that could lead to classification error. While many Veterans use VA care exclusively, there are Veterans who receive care outside the VA system. Dual system use to treat RA possibly differed between treatment groups, but in this analysis, the risk for dual system use was assumed to be small. There was no risk of observer bias. This study was limited to adult patients with at least 6 months enrollment before initiating therapy and activity in the system for $\geq$1 year after the index event. Any correlation between length of enrollment and choice of index biologic agent was unlikely.

In summary, adult patients with RA in the VA were significantly more likely to be persistent and adherent in taking TNFi + MTX combination therapy than in using triple therapy with nonbiologic DMARDs, based on 3 methods used to analyze persistence and a measure of adherence. Additional research is needed to determine the extent to which safety, efficacy, or other factors contribute to differences in persistence and adherence with TNFi + MTX or triple therapy.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Sauer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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