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BRIEF REPORT

Intensification to Triple Therapy After Treatment With Nonbiologic Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis in the United States From 2009 to 2014

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Objective. **Several trials suggest that triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) and biologic disease-modifying antirheumatic drugs (DMARDs) have similar efficacy in patients with rheumatoid arthritis (RA). This study was undertaken to investigate intensification to triple therapy after initial nonbiologic prescription among patients with RA.**

Methods. **The use of triple therapy among patients with RA in 2009–2014 was evaluated using US insurance claims data. Patients with a health care visit for RA and an initial nonbiologic DMARD prescription were included. Frequencies of intensification to triple therapy or a biologic DMARD and rates of intensification per 6-month time period were calculated. Using Cox regression, we evaluated whether sociodemographic, temporal, geographic, clinical, and health care utilization factors were associated with intensification to triple therapy. Among those patients whose therapy was intensified, we investigated factors associated with triple therapy use by logistic regression. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) for intensification to triple therapy in relation to various clinical and demographic factors were calculated.**

Results. **There were 24,576 patients with a mean ± SD age of 50.3 ± 12.3 years, and 78% were female. During the study period, treatment was intensified to biologic DMARDs in 2,739 patients (11.1%) compared to 181 patients (0.7%) whose treatment was intensified to triple therapy. There was no significant change in triple therapy use across calendar years. Patients whose treatment was intensified to triple therapy were more likely to receive glucocorticoids (HR 1.91 [95% CI 1.41–2.60]) compared to patients who did not use glucocorticoids and were more likely to use nonsteroidal antiinflammatory drugs (NSAIDs) (HR 1.48, 95% CI 1.10–1.99 versus no NSAID use). Among those patients whose treatment was intensified to triple therapy or biologic DMARDs, factors significantly associated with triple therapy use included older age, US region (with the highest odds for triple therapy use in the West and lowest odds for triple therapy use in the Northeast), glucocorticoid use, and lower number of outpatient visits within 180 days of initial nonbiologic DMARD prescription.**

Conclusion. **Despite reports published during the study period suggesting equivalent efficacy of triple therapy and biologic DMARDs for RA, the use of triple therapy was infrequent and did not increase over time in this large nationwide study.**

Several randomized controlled trials demonstrate that triple therapy (combination of methotrexate [MTX], sulfasalazine [SSZ], and hydroxychloroquine [HCQ]) is noninferior to biologic disease-modifying antirheumatic drugs (biologic DMARDs) for the treat-

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ment of rheumatoid arthritis (RA) (1–3). Compared to biologic DMARDs, triple therapy use has been shown to have superior cost effectiveness and similar quality-of-life measures (4–6).

Despite the growing number of biologic DMARDs for RA, triple therapy may have an important role in the treatment of RA by optimizing efficacy and cost. In part due to recent efforts advocating treatment to target remission for patients with RA, clinicians are now faced with complex treatment decisions for RA, balancing efficacy, safety, and cost for a variety of options for treatment with DMARDs (7). The 2012 American College of Rheumatology guidelines for RA treatment recommended triple therapy as a treatment option for patients with RA after failure of initial nonbiologic DMARD monotherapy, or as initial therapy for patients with high disease activity and poor prognosis (8). Moreover, initial treatment utilizing triple therapy at RA diagnosis may reduce disease activity compared to MTX monotherapy (9).

While the evidence supporting triple therapy is accumulating in randomized controlled trials, less is known about the use of triple therapy in typical clinical practice. A prior study using a national claims database evaluated adherence patterns with triple therapy treatment compared to treatment with etanercept and MTX, but previous studies have not investigated temporal trends for intensification to triple therapy or factors associated with receiving triple therapy (10). Factors including perceived efficacy, age, socioeconomic status, geography, comorbidities, previous infections, and health care utilization may influence whether a patient is prescribed triple therapy or other therapies such as biologic DMARDs. Therefore, we investigated the utilization of triple therapy and the factors associated with its use in a large nationwide insurance claims database. We aimed to quantify triple therapy use, assess temporal trends, and investigate whether factors are associated with triple therapy intensification for patients with RA in typical clinical practice.

PATIENTS AND METHODS

Data source. We conducted a study using insurance claims data from Aetna, a commercial US health plan, for the period of July 1, 2009 to June 30, 2014. This database contains longitudinal claims information including medical diagnoses, procedures, hospitalizations, physician visits, inpatient/infusion visits, and pharmacy dispensing among subscribers across the United States. Aggregate data on socioeconomic status and demographic composition were obtained by linking zip code of residence with data from the 2010 US Census. The Partners HealthCare Institutional Review Board approved the study protocol.

Study cohort. For inclusion in the analysis, patients had to have at least 1 prescription for a nonbiologic DMARD (MTX, SSZ, HCQ, leflunomide, azathioprine, mycophenolate mofetil, cyclosporine, gold, or D-penicillamine), 180 days of continuous enrollment prior to their first nonbiologic DMARD prescription, and at least 1 inpatient or outpatient diagnosis code for RA (*International Classification of Diseases, Ninth Revision* [ICD-9] code 714.xx) prior to and including the nonbiologic DMARD prescription date (11). The index date was the date of the first nonbiologic DMARD prescription meeting these criteria. Patients with prevalent RA at the index date were eligible to be in the study cohort. Since we investigated intensification to triple therapy or a biologic DMARD, we excluded patients whose first prescription was for a biologic DMARD.

Intensification to triple therapy or biologic DMARD. Triple therapy use was defined as prescriptions for MTX, SSZ, and HCQ within the same 60-day period. The start of triple therapy was established as the date when the prescription for the third of 3 medications was first filled, in conjunction with the other 2 medications. If a patient was prescribed triple therapy at the index date (180 days prior to prescription of a nonbiologic DMARD) or in the baseline period, we considered this an outcome occurring at the index date and the patient was excluded. We defined intensification to a biologic DMARD as the first prescription for a biologic DMARD (etanercept, adalimumab, infliximab, certolizumab pegol, golimumab, rituximab, abatacept, anakinra, tocilizumab, or tofacitinib) after the index nonbiologic DMARD. If a patient received both triple therapy and a biologic DMARD during follow-up, we considered the first intensification event as the outcome measure for this study.

We categorized the index nonbiologic DMARD as follows: at least 1 triple-therapy nonbiologic DMARD (MTX, SSZ, or HCQ), another nonbiologic DMARD in combination with 1 of the triple therapy nonbiologic DMARDs, or other nonbiologic DMARD monotherapy. We further classified nonbiologic DMARD as monotherapy or as combination (2 or more nonbiologic DMARDs prescribed at the index date).

Covariates. Sociodemographic, geographic, and temporal factors as of the index date were recorded as follows: sex, age, median annual household income in the patient's zip code ($<$\$50,000, \$50,000–\$99,999, or $\geq$\$100,000), US region (South, Northeast, West, or Midwest), and rural/urban residence. Age was further categorized as $<$40, 40-49, 50-59, or $\geq$60 years. Year of cohort entry and time to intensification were investigated as covariates.

Clinical and health care utilization factors within the 180 days before the index date were considered. Treatments considered included use of nonsteroidal antiinflammatory drugs (NSAIDs), opioids, and antibiotic, antifungal, and antiviral agents prior to the index date. We calculated the total number of unique prescriptions (excluding nonsystemic [topical] formulations). Comorbidities considered were asthma, chronic obstructive pulmonary disease, coronary artery disease, cancer (excluding nonmelanoma skin cancer), hypertension, ischemic stroke, congestive heart failure, depression, and diabetes mellitus. We also calculated a combined comorbidity score that combined conditions from the Charlson and Elixhauser measures (12). Additionally, we considered any hospitalization for serious infection (as previously validated [13]),

Table 1. Characteristics of the study subjects at the index date (n = 24,576)*

Sociodemographic factors	
Female	19,110 (77.8)
Age, mean ± SD years	50.3 ± 12.3
Age group, years	
<40	4,371 (17.8)
40–49	5,678 (23.1)
50–59	8,771 (35.7)
≥60	5,756 (23.4)
Median annual household income by zip code	
<$50,000	5,670 (24.0)
$50,000–$99,999	15,494 (65.6)
≥$100,000	2,463 (10.4)
Year of index date	
2009	7,594 (30.9)
2010	4,621 (18.8)
2011	3,947 (16.1)
2012	3,696 (15.0)
2013	3,380 (13.8)
2014†	1,338 (5.4)
Geographic factors	
US region of residence	
South	9,319 (39.4)
Northeast	6,404 (27.1)
West	5,726 (24.2)
Midwest	2,181 (9.2)
Rural/urban residence	1,884 (8.0)
Clinical factors‡	
Index nonbiologic DMARD	
MTX, SSZ, or HCQ	21,584 (87.8)
Other nonbiologic DMARD in combination with MTX, SSZ, or HCQ§	271 (1.1)
Other nonbiologic DMARD monotherapy	2,721 (11.1)
Combination nonbiologic DMARDs	4,157 (16.9)
Glucocorticoids	11,147 (45.4)
NSAIDs or coxibs	10,672 (43.4)
Opioids	7,465 (30.4)
Antibiotic	10,613 (43.2)
Antifungal	1,169 (4.8)
Antiviral	3,577 (14.6)
No. of unique prescriptions, mean ± SD	7.8 ± 4.8
Hospitalization for a serious infection	384 (1.6)
Asthma or chronic obstructive pulmonary disease	2,260 (9.2)
Coronary artery disease	1,024 (4.2)
Cancer	2,247 (9.1)
Hypertension	6,469 (26.3)
Ischemic stroke	313 (1.3)
Congestive heart failure	259 (1.1)
Depression	2,183 (8.9)
Diabetes mellitus	2,006 (8.2)
Combined comorbidity score, mean ± SD	0.2 ± 1.0
Health care utilization factors‡	
Rheumatologist appointment	8,816 (35.9)
No. of outpatient visits, mean ± SD	9.8 ± 8.4
No. of inpatient stays	
0	22,814 (92.8)
1	1,457 (5.9)
≥2	305 (1.2)
No. of emergency department visits	
0	23,129 (94.1)
1	930 (3.8)
≥2	517 (2.1)

* Except where indicated otherwise, values are the number (%) of patients (missing values not reported). MTX = methotrexate; SSZ = sulfasalazine; HCQ = hydroxychloroquine; NSAIDs = nonsteroidal antiinflammatory drugs.
† End of study period was June 30, 2014.
‡ Clinical and health care utilization factors were assessed within the 180 days before the index date.
§ Other nonbiologic disease-modifying antirheumatic drugs (DMARDs) were leflunomide, azathioprine, mycophenolate mofetil, cyclosporine, gold, and D-penicillamine.

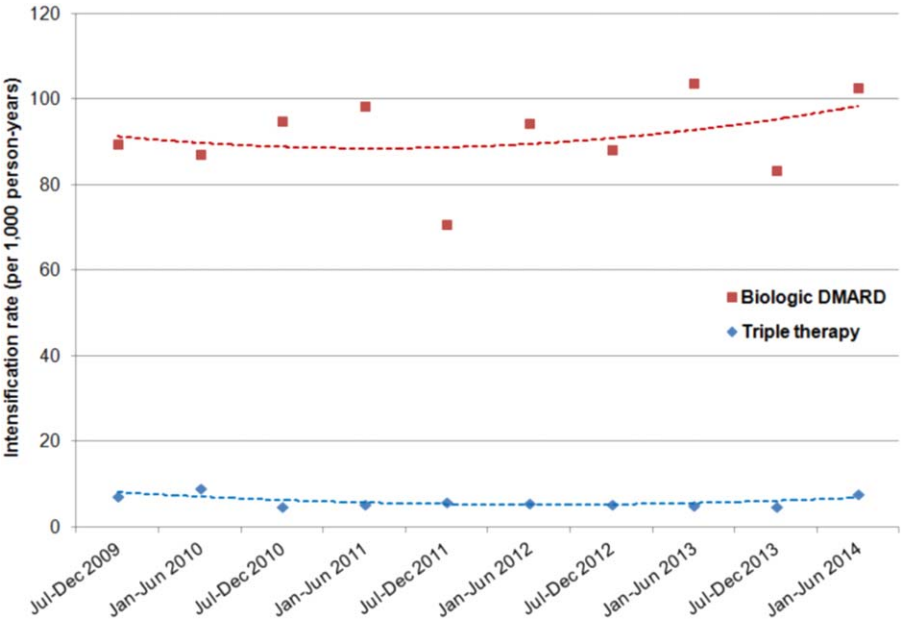

Figure 1. Rate of intensification to triple therapy (blue dashed line) and biologic disease-modifying antirheumatic drugs (DMARDs) (red dashed line) after initial prescription of a nonbiologic DMARD for rheumatoid arthritis, 2009–2014.

appointment with a rheumatologist, number of outpatient visits, and inpatient stays and emergency department visits (categorized as 0, 1, or ≥2).

Statistical analysis. We performed descriptive statistical analysis and unadjusted comparisons using chi-square tests for categorical variables and *t*-tests for continuous variables. We used Cox proportional hazards models to estimate hazard ratios (HRs) for treatment intensification to triple therapy. We initially performed unadjusted Cox models for each covariate described above to estimate HRs and 95% confidence intervals (95% CIs).

We built multivariable Cox regression models using forward stepwise selection of variables with *P* values of <0.1 as criteria for entry. The final model for analysis of associations with triple therapy utilization included US region of residence, index nonbiologic DMARD, combination nonbiologic DMARD (yes/no), glucocorticoid use, NSAID use, and number of outpatient visits.

We then restricted the sample to patients whose treatment was intensified to either triple therapy or biologic DMARD in order to investigate predictors for triple therapy use (as compared to biologic DMARD use) in this subgroup of such patients. We used logistic regression to estimate unadjusted odds ratios (ORs) and 95% CIs for triple therapy use based on sociodemographic, temporal, geographic, clinical, and health care utilization factors. We built multivariable logistic regression models using forward stepwise selection of variables with *P* values of <0.1 as criteria for entry. The final model for analysis of associations with triple therapy use among those who received intensified therapy consisted of age group, US region of residence, index nonbiologic DMARD, combination nonbiologic DMARD, glucocorticoid use, and number of outpatient visits. Since only those patients whose treatment was intensified to triple therapy and biologic DMARDs were included in this analysis, factors associated with increased use of triple therapy were inversely associated with biologic DMARD use (and vice versa).

We calculated rates (per 1,000 person-years) of intensification to triple therapy or biologic DMARD over 6-month periods (January–June and July–December) during the entire 60 months of the study. We plotted trend lines for triple therapy and biologic DMARD intensification rates using smoothing splines. We performed 2 sensitivity analyses with identical methods: in the first, the study sample was restricted to those who received at least 1 triple therapy nonbiologic DMARD by index date, and in the second the study sample was restricted to those with 2 or more ICD-9 codes for RA (714.xx).

Two-sided *P* values less than 0.05 were considered significant. All analyses were performed using SAS version 9.3 (SAS Institute).

RESULTS

A total of 24,576 patients with nonbiologic DMARD prescriptions for RA were analyzed. The mean ± SD age at the index date was 50.3 ± 12.3 years and 77.8% were female (Table 1). Of the study sample, the US region of residence where the largest percentage of patients resided was the South (39.4%) and the smallest percentage of patients resided in the Midwest (9.2%). The index nonbiologic DMARD was one of the 3 triple therapy DMARDs for most patients (87.8%) and most were receiving nonbiologic DMARD monotherapy (88.9%). The mean ± SD number of outpatient visits in the 180 days prior to index date was 9.8 ± 8.4.

Only 35.9% of the patients were seen by a rheumatologist within the 180 days before the index date.

There were a total of 2,739 patients (11.1%) whose treatment was intensified to biologic DMARDs and 181 patients (0.7%) whose treatment was intensified to triple therapy. The mean ± SD time to initiation of biologic DMARD treatment from index date was 320 ± 341 days and the mean ± SD time to triple therapy was 278 ± 298 days. Figure 1 shows temporal trends in intensification to biologic DMARD therapy and triple therapy. There was no significant change in the use of triple therapy over calendar periods during the study period (7/1/09–6/30/14). Among the entire study sample, the difference in temporal use of triple therapy approached significance only for the year 2013 versus 2009 (unadjusted HR 1.59 [95% CI 0.99–2.55]), but this was not included in the final multivariable model.

Patients initially prescribed combination nonbiologic DMARDs (HR 8.31 [95% CI 5.85–11.81]), glucocorticoids (HR 1.91 [95% CI 1.41–2.60]), or NSAIDs (HR 1.48 [95% CI 1.10–1.99]) were significantly more likely to receive triple therapy (Table 2). Compared to the South, patients in the Northeast were less likely to have their treatment intensified to triple therapy (HR 0.58 [95% CI 0.38–0.89]), although this was not statistically significant in the multivariable model (HR 0.66 [95% CI 0.43–1.02]). An increasing number of outpatient visits was associated with decreased risk of triple therapy use (HR 0.97 [95% CI 0.95–0.99]). Sex, age, area-level household income, year of index date, rural residence, serious infections, comorbidities, antimicrobial use, number of prescriptions, and rheumatologist appointments were not associated with intensification to triple therapy.

We also analyzed these factors among patients whose therapy was intensified to either triple therapy or biologic DMARD (n = 2,920). US geographic area was associated with triple therapy use among those patients whose treatment was intensified, i.e., increased risk in the West (OR 1.43 [95% CI 1.09–1.88]), decreased risk in the Northeast (OR 0.67 [95% CI 0.48–0.92]), and no significant difference in the Midwest (OR 1.26 [95% CI 0.85–1.86]) compared to residence in the South. Among patients whose treatment was intensified, there was a trend toward a greater likelihood of triple therapy with increasing age (multivariable OR 1.29 [95% CI 0.95–1.75], patients ≥60 years of age versus patients <40 years of age). Clinical factors that were significantly associated with triple therapy among patients whose therapy was intensified were as follows: at least 1 triple therapy nonbiologic DMARD at index date (OR 5.24 [95% CI 2.03–13.54]), combination nonbiologic DMARD at index date (OR 5.56 [95% CI 4.04–7.65]), and glucocorticoid use (OR 1.39 [95% CI 1.00–1.92]). Increasing number of outpatient visits was associated with decreased odds of receiving triple therapy (OR 0.95 [95% CI 0.92–0.98]). Year of index date was not significantly associated with triple therapy use among those whose therapy was intensified.

Results were similar when the analysis was restricted to patients whose initial therapy included at least one triple therapy nonbiologic DMARD (intensification to triple therapy in 0.8%) as well as when analysis was restricted to patients who had an ICD-9 code for RA on at least 2 visits (intensification to triple therapy in 0.9%). There was no increase in triple therapy use over calendar time. The number of outpatient visits and use of glucocorticoids or NSAIDs within 180 days of index date or prior were significantly associated with triple therapy use in these analyses.

DISCUSSION

Despite growing evidence indicating similar efficacy and reduced cost of triple therapy compared to biologic DMARDs (4,14), our large nationwide study demonstrates that triple therapy is used infrequently in routine clinical practice. According to our research, only 0.7–0.9% of patients with RA were prescribed triple therapy, even though 89% were initially prescribed MTX, SSZ, or HCQ. Of those patients whose therapy was intensified to biologic DMARDs or triple therapy, 93.8% of patients' treatments were intensified to biologic DMARDs. Our study period included the timeframe during which seminal randomized controlled trials demonstrating similar efficacy of triple therapy compared to biologic DMARDs were completed and the results published (1–3). We found no evidence that prescriptions of triple therapy subsequently increased. Even with guidelines advising treatment of RA to target remission or low disease activity, triple therapy use remained an infrequent choice of pharmacologic therapy for patients with RA throughout our study.

Using several strategies and noting previous research, we evaluated whether there was a temporal change in triple therapy use. The Swedish Pharmacotherapy (Swefot) trial was published in August 2009, the Treatment of Early Aggressive RA (TEAR) study was published in September 2012, and the RA Comparison of Active Therapies (RACAT) study was published in July 2013 (1–3). Notably, the Swefot trial demonstrated that infliximab and MTX were superior to triple therapy for RA efficacy at month 12, but not at months 6, 9, or 24 (3). Thus, some interpret these results as favoring combination of a biologic DMARD and MTX over triple therapy.

Table 2. Factors associated with intensification to triple therapy*

Characteristic	HRs for triple therapy intensification among the entire study sample (n = 24,576)		ORs for triple therapy use among those who intensified to triple therapy or biologic DMARD (n = 2,920)	
	Unadjusted HR (95% CI)	Multivariable HR (95% CI)	Unadjusted OR (95% CI)	Multivariable OR (95% CI)
Female	1.29 (0.88–1.88)	–	1.40 (0.95–2.07)	–
Age group				
<40 years	1.0 (referent)	–	1.0 (referent)	1.0 (referent)
40–49 years	1.25 (0.80–1.94)	–	1.04 (0.80–1.37)	1.01 (0.76–1.34)
50–59 years	1.24 (0.79–1.94)	–	1.20 (0.95–1.51)	1.23 (0.96–1.57)
≥60 years	0.95 (0.57–1.57)	–	1.22 (0.91–1.63)	1.29 (0.95–1.75)
Median annual household income by zip code				
<$50,000	1.0 (referent)	–	1.0 (referent)	–
$50,000–$99,999	0.95 (0.67–1.34)	–	1.13 (0.89–1.44)	–
≥$100,000	0.68 (0.37–1.24)	–	0.79 (0.54–1.15)	–
Year of index date				
2009	1.0 (referent)	–	1.0 (referent)	–
2010	0.72 (0.45–1.15)	–	0.66 (0.44–0.97)	–
2011	1.16 (0.76–1.78)	–	1.11 (0.78–1.59)	–
2012	1.25 (0.80–1.94)	–	0.91 (0.63–1.32)	–
2013	1.59 (0.99–2.55)	–	1.13 (0.76–1.67)	–
2014	1.69 (0.60–4.73)	–	1.17 (0.49–2.75)	–
US region of residence				
South	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Northeast	0.58 (0.38–0.89)	0.66 (0.43–1.02)	0.62 (0.45–0.84)	0.67 (0.48–0.92)
West	1.30 (0.92–1.84)	1.25 (0.88–1.77)	1.42 (1.09–1.84)	1.43 (1.09–1.88)
Midwest	1.18 (0.71–1.96)	1.16 (0.70–1.92)	1.33 (0.91–1.93)	1.26 (0.85–1.86)
Rural residence	1.17 (0.70–1.95)	–	1.01 (0.60–1.72)	–
Index nonbiologic DMARD				
MTX, SSZ, or HCQ	22.46 (3.16–159.80)	25.69 (3.59–183.73)	3.23 (1.26–8.28)	5.24 (2.03–13.54)
Other nonbiologic DMARD in combination with MTX, SSZ, or HCQ	8.49 (0.53–135.46)	2.59 (0.16–41.51)	1.86 (0.42–8.25)	0.89 (0.20–3.98)
Other nonbiologic DMARD monotherapy	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Combination nonbiologic DMARDs	5.17 (3.86–6.92)	8.31 (5.85–11.81)	5.30 (3.88–7.23)	5.56 (4.04–7.65)
Glucocorticoids	2.02 (1.50–2.73)	1.91 (1.41–2.60)	1.24 (0.91–1.69)	1.39 (1.00–1.92)
NSAIDs or coxibs	1.68 (1.25–2.25)	1.48 (1.10–1.99)	1.16 (0.86–1.58)	–
Opioids	1.14 (0.83–1.56)	–	0.80 (0.58–1.11)	–
Antibiotic	0.77 (0.57–1.04)	–	0.73 (0.53–1.00)	–
Antifungal	1.06 (0.54–2.08)	–	0.97 (0.49–1.94)	–
Antiviral	0.83 (0.53–1.30)	–	0.92 (0.58–1.45)	–
Unique prescriptions	1.01 (0.98–1.04)	–	0.99 (0.96–1.02)	–
Hospitalization for a serious infection	†	–	†	–
Asthma or chronic obstructive pulmonary disease	0.78 (0.45–1.38)	–	0.81 (0.45–1.45)	–
Coronary artery disease	0.91 (0.43–1.93)	–	1.15 (0.52–2.52)	–
Cancer	0.99 (0.60–1.64)	–	1.27 (0.75–2.13)	–
Hypertension	0.72 (0.51–1.03)	–	0.86 (0.59–1.24)	–
Ischemic stroke	†	–	†	–
Congestive heart failure	1.02 (0.25–4.12)	–	1.34 (0.31–5.74)	–
Depression	1.00 (0.59–1.70)	–	0.94 (0.54–1.62)	–
Diabetes mellitus	1.01 (0.59–1.70)	–	1.14 (0.66–1.98)	–
Combined comorbidity score	0.99 (0.85–1.15)	–	1.08 (0.91–1.28)	–
Rheumatologist appointment	1.31 (0.97–1.76)	–	0.98 (0.72–1.33)	–
Outpatient visits	0.97 (0.95–0.99)	0.97 (0.95–0.99)	0.95 (0.93–0.98)	0.95 (0.92–0.98)

* HR = hazard ratio; 95% CI = 95% confidence interval; OR = odds ratio (see Table 1 for other definitions).
† Model did not converge.

We investigated whether the calendar year at index date was associated with intensification to triple therapy. Use in the year 2013 approached statistical significance (unadjusted HR 1.59 [95% CI 0.99–2.55]) compared to 2009, but the difference was not statistically significant in multivariable models. When analyses were restricted to only those patients whose treatment was intensified to triple therapy or to a biologic DMARD, there was no significant association for any year compared to 2009. We also investigated rates of intensification at 6-month intervals throughout the entire study period and found no increased rate of triple therapy use. Comparison of before and after publication dates of the RACAT and TEAR studies also showed no increase in prescriptions of triple therapy. Many of the reports describing superior cost-effectiveness and similar quality-of-life measures with triple therapy compared to biologic DMARDs were published near the end of our study period, so they may not have been able to influence the increase in triple therapy use in a clinical setting (4,6). Since the index date in our study was the date of the first nonbiologic DMARD prescription for each patient, we were able to replicate a cohort of patients with early RA receiving initial nonbiologic DMARD therapy, in whom later triple therapy use may have been indicated. Since we had longitudinal data, the index date also captured the time period of patients with early RA so that we could accurately investigate secular trends of triple therapy use.

We examined a variety of factors to assess predictors of triple therapy use and hypothesized that sociodemographic, geographic, and clinical factors may make physicians less inclined to prescribe triple therapy. US region of residence was a significant factor in determining triple therapy use. In particular among those patients whose treatment was intensified, residence in the Northeast was associated with 33% less use of triple therapy compared to residence in the South. Residence in the West and Midwest were associated with increased triple therapy use (HR 1.43 and 1.26, respectively). Rural residence and area-level household income were not associated with triple therapy use. There was also a trend toward an association of increasing age with triple therapy use. However, neither comorbidities nor a combined comorbidity score were associated with triple therapy use. RA patients who received glucocorticoids in the 180 days prior to the index date were more likely to receive triple therapy, in the analysis of the entire study sample, as well as the analysis only of those whose treatment was intensified to triple therapy. Patients who are treated with glucocorticoids shortly after RA diagnosis may have a more severe disease course. However, it is unclear why these patients were more likely to subsequently receive triple therapy than biologic DMARDs. Despite the risk of serious infections with biologic DMARDs (15), patients who received antimicrobial agents or had serious infections prior to the index date were not more likely to receive triple therapy.

The infrequent use of triple therapy demonstrated in our study may be due to several factors. Regional differences, glucocorticoid use, and number of outpatient visits were significant predictors for prescription of triple therapy in this analysis. Due to a low number of triple-therapy outcomes, our ability to analyze smaller geographic units or time periods was limited. Clinical trials directly comparing triple therapy and biologic DMARDs have primarily focused on efficacy outcomes, with secondary analyses for other outcomes such as work loss and side effects. In analyses using data from the Swefot trial, those patients who were randomized to receive triple therapy had less work loss compared to those patients who were randomized to receive infliximab and MTX (although the difference was not statistically significant) (4). In the RACAT study, patients treated with triple therapy had a significantly increased frequency of gastrointestinal side effects compared to those who were prescribed etanercept and MTX, but the frequency of serious gastrointestinal side effects was similar in both groups (2). Patients treated with etanercept and MTX had higher rates of serious infections compared to those treated with triple therapy (2). Research directly comparing triple therapy with biologic DMARDs for outcomes other than efficacy may further elucidate factors that affect preferences for triple therapy or biologic DMARDs among patients and clinicians.

Few previous studies have investigated triple therapy use in the routine clinical setting. Results of a recent study using insurance claims data suggested that patients responded better to combination etanercept and MTX than to triple therapy (10). This is in contrast to reports, from randomized controlled trials, of similar or even enhanced response to triple therapy compared to biologic DMARDs and highlights how findings from these trials do not always generalize to patients seen in typical clinical practice. Our study could not address whether concerns about prescription adherence were associated with a physician's likelihood of prescribing triple therapy. However, we did examine a variety of health care utilization factors. An increase in the number of outpatient visits was inversely associated with intensification to triple therapy. Patients requiring many appointments may have had a more severe RA disease course that prompted prescription of biologic DMARDs by the treating clinicians. However, other health care utilization

factors, such as rheumatologist appointments and emergency department visits, were not associated with triple therapy use.

It is important to note that there were several limitations to the study. Since our study included insurance beneficiaries throughout the entire US, our findings may reflect routine clinical care for patients with RA. However, because all of the patients in our study were insured, the findings may not be generalizable to underinsured or uninsured patients, for whom generic oral drugs may be a preferable option. While we did not have access to clinical notes to verify RA diagnosis, we used methods with previously demonstrated validity (11). We were not able to evaluate some factors that may have influenced the decision to prescribe triple therapy, such as functional status, disease activity, erosions, deformities, lifestyle, and previous side effects from nonbiologic DMARDs. Since we used administrative claims data for analyses, we were unable to determine whether patients were being prescribed triple therapy or switching between nonbiologic DMARDs. Therefore, our findings may have actually overestimated the rate of triple therapy use. Given our finding of infrequent use of triple therapy, however, this limitation would not change the implications of our study.

In conclusion, we demonstrated that triple therapy was used infrequently in this large nationwide study of RA patients seen in routine clinical settings. We identified several factors associated with triple therapy use, such as region of residence, number of outpatient visits, and use of glucocorticoids. The use of triple therapy in typical clinical practice in the US remains low despite the data showing that triple therapy is noninferior to biologic DMARDs in RA patients with active disease after initial monotherapy with nonbiologic DMARDs such as MTX. Future studies investigating barriers to and facilitators of triple therapy use in RA are warranted.

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 published. Dr. Sparks 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.

Study conception and design. Sparks, Shrank, Solomon.

Acquisition of data. Sparks, Krumme, Shrank, Pezalla, Choudhry, Solomon.

Analysis and interpretation of data. Sparks, Krumme, Shrank, Matlin, Brill, Pezalla, Choudhry, Solomon.

ADDITIONAL DISCLOSURES

Authors Shrank and Matlin are employees of CVS Health. Author Pezalla is an employee of Aetna.

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