Assessment of Adherence to and Persistence on Disease-Modifying Antirheumatic Drugs (DMARDs) in Patients With Rheumatoid Arthritis

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Objective: Biologic disease-modifying antirheumatic drugs (DMARDs) are efficacious for treating rheumatoid arthritis (RA). However, measurements of relative effectiveness, including treatment adherence and persistence, are lacking. We evaluated adherence and persistence during new episodes of use of traditional and biologic DMARDs.

Methods: Using Tennessee Medicaid databases (1995–2004), we assembled a retrospective cohort of patients diagnosed with RA, and identified new episodes of use for 12 DMARD regimens. We evaluated persistence through survival analyses, and adherence within episodes through the medication possession ratio. A risk score was included in the analyses to account for measured confounders.

Results: We identified 14,932 patients with RA; 6018 patients had 10,547 episodes of new use of DMARDs. Considering methotrexate as the reference and after adjustment for measured confounders, episodes of new use of sulfasalazine [adjusted hazard ratio (aHR) = 1.59; 95% confidence interval (CI) = 1.47–1.72] and infliximab alone (aHR = 1.37, 95% CI = 1.09–1.73) were more likely to be discontinued; and new episodes of etanercept (aHR = 0.82, 95% CI = 0.73–0.92) and methotrexate + adalimumab (aHR = 0.63, 95% CI = 0.48–0.84) were less likely to be discontinued. Compared with methotrexate, adherence was higher for leflunomide, infliximab, etanercept, and adalimumab and lower for sulfasalazine and all combined therapies.

Conclusions: We developed an approach to assess persistence on and adherence to the most common DMARD therapies. In this large cohort, persistence and adherence to leflunomide and most biologic DMARD therapies were at least comparable to methotrexate. Adherence was lower for sulfasalazine and all combined therapies.

Key Words: rheumatoid arthritis, disease-modifying antirheumatic drugs

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Rheumatoid arthritis (RA) is associated with progressive disability and premature mortality.[1–3] Appropriate treatment can prevent or limit joint damage, prevent loss of function, decrease pain, and improve quality of life.[3–6] Traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, hydroxychloroquine, and sulfasalazine, are considered the foundation of RA treatment.[3] More recently, "biologic" DMARDs have been approved for use. These drugs include tumor necrosis factor antagonists (anti-TNF) and an interleukin-1 antagonist (anti-IL-1). Clinical trials have shown that these medications improve symptoms and retard disease progression.[7–11]

Nonetheless, clinical trials have some limitations.[12] Strict selection criteria limit generalization of results[13]; most trials are of short duration[3]; and sample size constraints limit their ability to identify infrequent adverse effects.[12–14] Finally, the experimental characteristics of these studies enhance medication adherence. In routine clinical practice, however, adherence to chronic therapy is often suboptimal.[15–17]

Because the full benefit of effective therapies can be achieved only if patients follow treatment regimens closely, adherence to and persistence on pharmacological treatments are crucial in the evaluation of relative effectiveness.[18,19] Although controversy regarding terminology persists,[20] adherence commonly refers to whether the patient takes a medication according to prescription, whereas persistence indicates time from initiation to discontinuation of therapy.[19] Overall, persistence reflects clinical effectiveness, occurrence of adverse effects, and/or patient and provider preferences.[21]

Nonadherence to and discontinuation of pharmacological therapies are important contributors to treatment failure, delayed recovery, accelerated progression of disease, and the

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need for more aggressive treatment. This can increase treatment-induced complications,[22,23] healthcare utilization, and related costs.[22,24,25] Information from postmarketing observational studies is needed to complement clinical trials data and clear definitions of effectiveness measures are necessary to enable comparisons between populations. We developed definitions for adherence and persistence on DMARD therapies for computerized administrative records and examined these measures among TennCare enrollees, a population typically excluded from clinical trials.

METHODS

Cohort Assembly

TennCare, the state-based capitated model program in Tennessee, covers those who are Medicaid-eligible and those who are uninsured or lack other access to health care. Using TennCare files we assembled a retrospective cohort of patients with RA. From January 1, 1995 through December 31, 2004, we identified all TennCare enrollees at least 18 years of age who had a diagnosis of RA (ICD9-CM: 714.0, 714.1, 714.2, 714.3, 714.30, 714.31, 714.32, 714.33, 714.4, 714.81). Eligible patients entered into the cohort when they met at least 1 of 3 selection criteria: (1) a hospitalization with a discharge diagnosis of RA; (2) at least 1 ambulatory visit with a diagnosis of RA and at least 1 prescription for a DMARD; or (3) at least 2 ambulatory visits separated by at least 1 month with a diagnosis of RA.[26]

Potential cohort members were required to have known gender and at least 365 days of continuous enrollment before entering into the cohort, to allow the collection of baseline characteristics. To limit other potential sources of poor persistence and adherence, we excluded patients with established serious medical conditions identified during the year before the cohort inception. These conditions were solid organ transplantation, HIV/AIDS, cancer (except nonmelanoma skin cancers), and serious renal, liver, or respiratory diseases. Cohort members were also required to have at least 1 prescription filled during that screening period to assure access to medication benefits.

An annual cross-sectional evaluation of DMARD use determined that at least 85% of the observed patterns were represented by 12 regimens: methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, etanercept, infliximab, adalimumab; and the combined therapies: methotrexate + infliximab, methotrexate + etanercept, methotrexate + adalimumab, methotrexate + hydroxychloroquine; and anakinra or methotrexate + anakinra. Patients who filled 1 or more prescriptions for these regimens were the subjects of this study.

Cohort members were followed from the date when the selection criteria were met to the end of the study (December 31, 2004), date of death, date of diagnosis of a serious medical condition, or loss of enrollment from TennCare, whichever came earliest.

New Episodes of DMARD Therapies

An episode of use started on the date when a DMARD prescription was filled and ended when the last prescription fill was expected to be exhausted, based on the days of drug supply recorded in the pharmacy files. Under TennCare mandate, prescriptions are generally filled for a time interval no longer than 30 days. Within episodes of use, we allowed short periods, that is, gaps (defined as less than or equal to 90 days) without medication available. An episode of use ended on the date of death, loss of enrollment, diagnosis of serious illness, stopping a specific DMARD (greater than 90 days without supply of drug), change to a different DMARD regimen (including nonstudy DMARDs), or end of study period, whichever came first.

Some DMARD regimens involved 2 different medications. For these regimens, an episode of use started when both drugs became available simultaneously, that is, when the patient filled a joint prescription for both medications on the same date, or when a new medication was added to ongoing therapy. Lack of a subsequent prescription for the ongoing therapy after the addition of a new medication was considered evidence of switching to a new therapy, rather than the use of combined therapy. In this situation, the new episode of use started on the date the new medication was filled. For each combined treatment, gaps for either medication were considered as gaps for the episode of use. The discontinuation of either of the drugs determined the end of the episode.

Tracking filled prescriptions from computerized pharmacy records is a valid method to measure drug utilization[18,25,27–29] and persistence on specific DMARD therapies was examined by estimating the time to treatment discontinuation.[19] We evaluated the overall persistence on DMARD therapies, which represented the combination of 2 outcomes: (1) time to stopping a DMARD regimen, cessation of therapy for at least 90 days without the addition of an alternate DMARD; and (2) time to switching to a different DMARD regimen. Although previous studies of NSAIDs use applied similar 90 days periods to define drug discontinuation,[30] no standard definition for DMARD discontinuation exists. We applied a conservative 90-day threshold to define drug discontinuation in this study.

We examined adherence to DMARD therapies within episodes by calculating the medication possession ratio (MPR).[19,25] The MPR represents the proportion of days supply obtained during 1 episode of medication use; we calculated it by dividing the aggregated number of days supply obtained during the episode by the length of the episode, excluding the last prescription fill.[19,25] Thus, episodes that included only 1 prescription were excluded from these calculations. Examining the use of concurrent medications could help in assessing the degree of disease control accomplished by DMARD therapies. Although DMARDs can control disease activity, pain control might require additional treatment.[31] Accordingly, the concurrent utilization of narcotics, corticosteroids, and NSAIDs during episodes of DMARD use was estimated dividing their aggregated days supply by the length of the episode.

Because measurements of persistence and adherence for chronic users of DMARDs would be expected to be higher than for those patients initiating these therapies, we restricted our evaluation to new users of DMARDs.[32] Cohort

members were required to have at least 365 days free of the specific DMARD before beginning an episode. Data on medication use during hospitalizations are not available in TennCare databases and days in the hospital were not included in these analyses.

Analysis

Summary Risk Score

We identified factors potentially affecting treatment adherence and persistence during the 365 days before the beginning of each new episode of use. Information was collected on: (1) health care utilization data, including number of hospitalizations, outpatient and emergency room visits, and number of different medication prescriptions filled; (2) the number of prescriptions filled and days of drug supply for DMARDs, oral corticosteroids, NSAIDs, and narcotics; and (3) specific dichotomous variables, indicating the utilization of anticonvulsants, bronchodilators, antipsychotics, antidepressants, sedatives and hypnotics, antihypertensives, gastroprotective medications (proton pump inhibitors and histamine-2 receptor antagonists), antiarrhythmics, anticoagulants, aspirin and other platelet inhibitors, antidiabetics, antimicrobials, digoxin, lipid-lowering agents, loop diuretics, and nitrates. We also assessed clinical diagnoses including chronic obstructive pulmonary disease, congestive heart failure, myocardial infarction, angina, rheumatic heart disease, atrial fibrillation, smoking-related diagnoses, excessive alcohol consumption, cerebrovascular disease, hypertension, and diabetes.

To account for measured confounders and to reduce the number of covariates in the regression models, we created a summary risk score.[33–36] For evaluations of persistence, we fit Cox proportional hazards models relating our respective outcomes to the covariates, restricted to episodes of methotrexate use. Methotrexate has been shown to be equivalent or superior in efficacy to other traditional DMARDs, slows the radiographic progression of disease,[37–39] and served as the reference medication for comparison purposes. From the fitted models, we computed the linear predictor for each cohort member and categorized it into quintiles. The lowest quintile represented patients with the lowest risk for developing the specific outcome of interest. The risk of developing the outcome increased with increasing quintiles. When compared with the lowest quintile, the highest quintile was associated with a rate ratio of 3.0 for stopping DMARD use and 4.3 for switching to a different DMARD. The same procedure was used to derive a risk score for adherence using multiple linear regression models. The risk scores, together with the exposure, were included in the final multivariate models.[33]

Persistence and Adherence

For evaluations of persistence, we used Cox regression models to estimate hazard ratios and 95% confidence intervals after adjustment for age, sex, race, calendar year, residence location, disability, residency in nursing home, and the risk score. Patients could contribute more than 1 episode of use of the same regimen, as long as they met our definition of new user. An entire new set of covariates was obtained for each subsequent episode and we accounted for multiple episodes per patient, calculating robust standard errors.[40]

We used multiple linear regression models to assess adherence to DMARD therapies while adjusting for measured confounders. As with assessing persistence, robust standard errors were calculated. All fitted models were evaluated through standard diagnostic procedures and no major departures from model assumptions were observed. Analyses were performed in Stata version 9.0 (StataCorp., College Station, TX). The study protocol was approved by the Institutional Review Board of Vanderbilt University Medical Center and informed consent was waived.

RESULTS

Rheumatoid Arthritis Cohort

Within the study period 2,915,378 TennCare enrollees were potentially eligible and 26,837 (0.9%) met our definition of RA. We required patients to be at least 18 years of age and to have 365 days of continuous enrollment before the first diagnosis of RA was made; these criteria excluded 9409 subjects (35%). After excluding patients without at least 1 prescription filled before cohort entry (n = 1259) and those with serious medical conditions (n = 1237), our cohort included 14,932 RA patients.

In our cohort, 2817 patients (19%) had a documented discharge diagnosis of RA; 5172 (35%) had at least 1 ambulatory visit coded as RA and 1 filled prescription for a DMARD; and 6943 patients (46%) had at least 2 ambulatory visits coded as RA.

New Episodes of DMARD Use

We identified 10,547 episodes of new use of DMARD therapies in 6018 patients, 40% of the RA cohort. The median number of episodes per patient was 1 (range, 1–12). New users were mostly female (80%) and white (72%). New users of biologic DMARDs tended to be older and more likely to have recorded disabilities than new users of traditional DMARDs. The median number of emergency room visits during the year before the beginning of the episodes was similar among new users of different DMARD therapies, whereas the median number of hospitalizations and outpatient visits was higher among users of leflunomide and biologic DMARDs than among users of traditional DMARDs. New users of biologic DMARDs had more prescriptions filled for different types of drugs than users of traditional DMARDs. Patients starting new episodes of biologic therapies had received more DMARDs, corticosteroids, narcotics, and NSAIDs than new users of traditional DMARDs or leflunomide (Table 1).

The most common DMARD therapies were methotrexate (37%), hydroxychloroquine (30%), and methotrexate + hydroxychloroquine (9%). Sulfasalazine and leflunomide therapies represented 9% and 5% of the total, respectively. Biologic DMARDs accounted for 10% of episodes. Etanercept alone, or combined with methotrexate, was the most commonly used biologic DMARD, followed by adalimumab and infliximab. There were 75 episodes of new use (0.7%) of

TABLE 1. Baseline Profile of New Episodes of DMARD Use. TennCare Rheumatoid Arthritis Cohort

	MTX	HYD	SULF	LEF	MTX + HYD	INF	ETA	ADA	MTX + INF	MTX + ETA	MTX + ADA	ANA, MTX + ANA	*P*
No. new episodes	3859	3174	944	558	904	75	374	120	98	262	107	72	—
Age*	54 (44–63)	51 (42–61)	51 (41–60)	55 (45–63)	52 (43–60)	53 (41–60)	51 (42–59)	58 (49–66)	56 (46–62)	53 (45–62)	58 (50–65)	53 (46–61)	0.0001
Gender†													<0.001
Female	78.1	82.7	71.2	79.4	84.2	74.7	77.5	80.8	76.5	83.6	79.4	72.2	—
Race													<0.001
White	72.4	71.2	76.5	72	69.9	66.7	70.9	64.2	72.4	64.9	61.7	63.9	—
Black	15.5	17.3	12.9	14.9	18.3	16	14.4	16.7	12.2	14.1	21.5	13.9	—
Other	12.1	11.5	10.6	13.1	11.8	17.3	14.7	19.2	15.3	21	16.8	22.2	—
Location													0.005
Major metropolitan areas	53.8	52.5	53.1	50.9	53.1	34.7	44.7	44.2	44.9	49.2	55.1	51.4	—
Other SMSA	25.4	23.7	23.5	25.8	22.6	33.3	24.1	22.5	26.5	27.1	20.6	27.8	—
Rural	20.7	23.8	23.4	23.3	24.3	32	31.3	33.3	28.6	23.7	24.3	20.8	—
Nursing home resident	0.9	0.6	0.5	0.5	0.1	0	0.8	0	0	0.4	0	1.4	0.37
Disability	55.9	53.2	54.3	61.3	58.8	72	69.3	70	73.5	68.7	66.4	68.1	<0.001
Healthcare use during last year*													
Hospital admissions	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0.0308
Outpatient clinic visits	10 (6–16)	10 (6–16)	10 (6–16)	11 (6–17)	11 (7–16)	13 (7–18)	13 (8–19)	15 (8–22)	15 (11–20)	13 (8–19)	13 (9–18)	14 (9–19)	0.0001
Emergency department visits	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	0 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	0 (0–2)	1 (0–2)	0 (0–2)	0 (0–1)	0.829
Medication use during last year*													
No. different drugs	16 (10–24)	16 (10–23)	15 (10–22)	19 (13–25)	18 (12–25)	22 (13–28)	20 (14–28)	25 (19–36)	22 (17–29)	21 (14–28)	24 (17–30)	21 (13–28)	0.0001
DMARD, prescriptions filled‡	0 (0–1)	0 (0–0)	0 (0–2)	4 (0–12)	7 (3–11)	7 (0–19)	7 (1–16)	8 (2–16)	12 (8–15)	12 (8–16)	13 (9–19)	12 (4–16)	0.0001
DMARD, days supply‡	0 (0–16)	0 (0–0)	0 (0–54)	102 (0–261)	176 (74–292)	152 (0–325)	166 (28–304)	181 (30–304)	264 (165–328)	267 (182–333)	275 (159–336)	250 (92–317)	0.0001
Oral corticosteroids, days supply	13 (0–73)	7 (0–56)	10 (0–81)	79 (7–253)	47 (0–182)	73 (0–236)	67 (0–245)	111 (6–253)	99 (10–249)	122 (13–266)	136 (30–236)	141 (30–281)	0.0001
Narcotics, prescriptions filled	4 (1–12)	4 (1–11)	3 (1–11)	6 (1–13)	5 (1–12)	9 (1–18)	8 (2–16)	13 (5–20)	11 (3–16)	8 (2–16)	12 (2–21)	12 (4–18)	0.0001
Narcotics, days supply	34 (4–149)	27 (3–130)	26 (2–121)	66 (9–225)	48 (7–175)	120 (10–264)	97 (15–256)	205 (66–331)	141 (37–296)	111 (21–254)	193 (34–318)	217 (64–335)	0.0001
NSAIDs, prescriptions filled	4 (1–8)	3 (0–8)	3 (0–8)	5 (0–10)	5 (1–10)	2 (0–8)	5 (0–10)	4 (0–10)	6 (1–12)	5 (0–11)	6 (1–12)	4 (0–11)	0.0001
NSAIDs, days supply	74 (10–189)	61 (3–175)	61 (4–191)	101 (0–250)	102 (10–232)	54 (0–181)	120 (0–244)	100 (0–252)	151 (30–298)	127 (0–272)	147 (6–286)	65 (0–277)	0.0001
Other medication use during last year†													
Anticonvulsants	17.5	16.5	15.6	15.4	16	25.3	21.7	28.3	24.5	17.2	23.4	20.8	0.001
Bronchodilators	28.3	28.8	26	32.4	27.7	25.3	29.4	34.2	35.7	28.2	32.7	26.4	0.245
Antipsychotics	7.5	6.9	6.6	5.9	6.9	10.7	8	19.2	11.2	7.6	10.3	5.6	<0.001
Antidepressants	51.1	51.6	50.5	48.9	52.9	57.3	58.6	65	63.3	58	59.8	59.7	0.001
Sedatives	22	22.2	20.2	20.4	19.8	24	24.3	25.8	18.4	23.3	23.4	20.8	0.672
ACE inhibitors	28.5	27.6	25.1	31	28.2	26.7	30.2	44.2	44.9	29	45.8	29.2	<0.001
Calcium channel blockers	22.6	21.6	20.9	21	20.2	14.7	19.5	21.7	18.4	18.3	18.7	16.7	0.497
Thiazides	23.1	22.6	20.1	22.6	21.9	22.7	18.2	26.7	26.5	18.7	30.8	12.5	0.038
Other antihypertensives	8.2	7.6	6.9	9.9	6.7	8	7.8	13.3	7.1	7.6	9.3	13.9	0.163
Gastroprotective drugs	55.2	55.5	56	64	59.6	58.7	65.5	65.8	57.1	64.1	63.6	63.9	<0.001
Antiarrhythmics	23.5	22.7	21.7	23.5	21	21.3	22.2	30.8	28.6	25.6	29.9	26.4	0.229

(*Continued*)

TABLE 1. (*Continued*)

	MTX	HYD	SULF	LEF	MTX + HYD	INF	ETA	ADA	MTX + INF	MTX + ETA	MTX + ADA	ANA, MTX + ANA	*P*
	MTX	HYD	SULF	LEF	MTX +HYD	INF	ETA	ADA	MTX +INF	MTX +ETA	MTX +ADA	ANA, MTX+ ANA	*P*
Anticoagulants	4.7	5.1	2.9	5.6	4.1	5.3	4.3	9.2	6.1	4.6	6.5	4.2	0.119
Aspirin	10.3	8.8	8.7	11.5	11.4	9.3	11.2	9.2	11.2	10.7	11.2	13.9	0.267
Other platelet inhibitors	4.4	3.4	3.3	5	2.2	4	7	13.3	7.1	7.6	11.2	9.7	<0.001
Antidiabetics	16.6	14.6	13	21	17.3	16	18.4	23.3	18.4	16.4	16.8	26.4	<0.001
Antimicrobials	78.6	80.2	82.1	80.6	78.1	76	84.2	85.8	83.7	84	81.3	83.3	0.031
Digoxin	4.6	4.7	3.8	5.2	3.7	2.7	3.5	2.5	3.1	3.1	1.9	1.4	0.462
Lipid-lowering drugs	22.2	19.6	20.9	22.9	19.4	26.7	25.1	42.5	20.4	28.6	39.3	20.8	<0.001
Loop diuretics	22.3	21.6	19.1	25.3	22.8	21.3	25.1	30.8	31.6	27.9	24.3	23.6	0.006
Nitrates	11.6	10.1	11.3	12.7	11.8	6.7	10.4	11.7	11.2	10.7	8.4	12.5	0.605
Medical diagnoses reported during last year†													
COPD	27.6	28.1	26.6	29.6	25.2	26.7	31.6	33.3	33.7	30.2	30.8	26.4	0.357
CHF	8	7.2	5.5	9.3	5.2	8	6.7	8.3	9.2	8.4	3.7	5.6	0.043
MI	2.6	1.6	2.6	3.8	1.9	1.3	4.5	2.5	3.1	3.8	2.8	2.8	0.011
Angina	5.6	4.3	6.1	5.6	4.9	2.7	4.5	7.5	6.1	5.7	10.3	8.3	0.088
Rheumatic valvulopathy	2.1	2.7	2.4	3.2	2.1	1.3	1.1	1.7	3.1	0.8	1.9	1.4	0.332
Atrial fibrillation	1.9	2.5	1.6	2	2.2	2.7	1.6	2.5	1	2.3	2.8	1.4	0.885
Smoking-related disease	8	6.9	7.2	10.8	8.4	17.3	12.6	13.3	11.2	14.5	12.1	11.1	<0.001
Excessive alcohol consumption	0.8	0.9	1	1.8	0.8	0	1.9	0	0	0	0	1.4	0.152
Hypertension	45.6	41.6	39	44.6	39.3	42.7	47.6	62.5	55.1	47.3	61.7	40.3	<0.001
Cerebrovascular disease	4.1	4.5	3.6	2.9	3.1	4	4.8	9.2	3.1	2.7	5.6	6.9	0.071
Diabetes	18.9	17	14.2	22	18.4	20	20.9	26.7	21.4	18.3	19.6	30.6	<0.001

*Median, (IQR) and *P* values for Kruskal–Wallis tests for marked row/section.

†Proportions and *P* values for χ^2 tests, unless otherwise specified.

‡Other than DMARD(s) of interest.

MTX indicates methotrexate; HYD, hydroxychloroquine; SULF, sulfasalazine; LEF, leflunomide; INF, infliximab; ETA, etanercept; ADA, adalimumab; ANA, anakinra; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; MI, myocardial infarction.

infliximab alone; anakinra or anakinra combined with methotrexate represented 0.7% of the total.

Overall Persistence on DMARD Therapies

Of 10,547 new episodes of DMARD use, 8835 (84%) were discontinued because of stopping or switching. Considering methotrexate as the reference and after adjustment for measured confounders, episodes of sulfasalazine [Adjusted hazard ratio (aHR) = 1.59, 95% confidence interval (CI) = 1.47–1.72, $P < 0.001$] and infliximab alone (aHR = 1.37, 95% CI = 1.09–1.73, $P = 0.007$) were more likely to be discontinued. On the other hand, episodes of etanercept (aHR = 0.82, 95% CI = 0.73–0.92, $P = 0.001$) and methotrexate + adalimumab (aHR = 0.63, 95% CI = 0.48–0.84, $P = 0.002$) were less likely to be discontinued (Fig. 1 and Table 2).

New users of infliximab alone were at higher risk of discontinuation compared with new users of infliximab + methotrexate (aHR = 1.5, 95% CI = 1.1–2.04, $P = 0.01$). The main cause of discontinuation among infliximab users was switching to a different regimen. In contrast, etanercept regimens were less likely to result in discontinuation than the combination of etanercept + methotrexate (aHR = 0.8, 95% CI = 0.67–0.97, $P = 0.022$).

Time to Stop Filling DMARD Prescriptions

Patients stopped filling their prescriptions for more than 90 days without switching to a different DMARD regimen in 5649 episodes, 54% of the total. Compared with users of methotrexate, users of sulfasalazine were more likely to stop filling their prescriptions (aHR = 1.67, 95% CI = 1.53–1.82, $P < 0.001$). In contrast, users of etanercept, methotrexate + etanercept or anakinra or methotrexate + anakinra were less likely to stop filling their DMARD prescriptions (Table 2).

Etanercept alone was more likely to result in stopping than the combination of methotrexate + etanercept (aHR = 14.7, 95% CI = 6.03–36.09, $P < 0.001$).

Time to Switch to a Different DMARD Therapy

During the study period, 3186 episodes (30%) of use of DMARD therapies resulted in a switch to a different DMARD regimen. When compared with methotrexate, infliximab alone or any combined therapy was more likely to be switched to a different DMARD regimen (Table 2).

Most episodes of use of infliximab that were switched to a different regimen (65%) resulted in the addition of methotrexate. Episodes of use of infliximab and the combination of methotrexate + infliximab were equally likely to result in switching (aHR = 0.96, 95% CI = 0.65–1.42, $P = 0.857$). In contrast, use of etanercept alone was less likely to result in switching, compared with use of methotrexate + etanercept (aHR = 0.47, 95% CI = 0.37–0.58, $P < 0.001$).

Switching from combined therapies usually resulted in the continuation of either medication alone. Among 772 episodes of methotrexate + hydroxychloroquine that ended in a switch to a new regimen, 317 (41%) and 315 (41%) continued on methotrexate and hydroxychloroquine, respectively. Among 69 episodes of methotrexate + infliximab that resulted in switching, 40 (58%) continued on methotrexate and 18 (26%) on infliximab. Similarly, among 198 episodes of methotrexate + etanercept that were switched, 77 (39%) continued on methotrexate, whereas

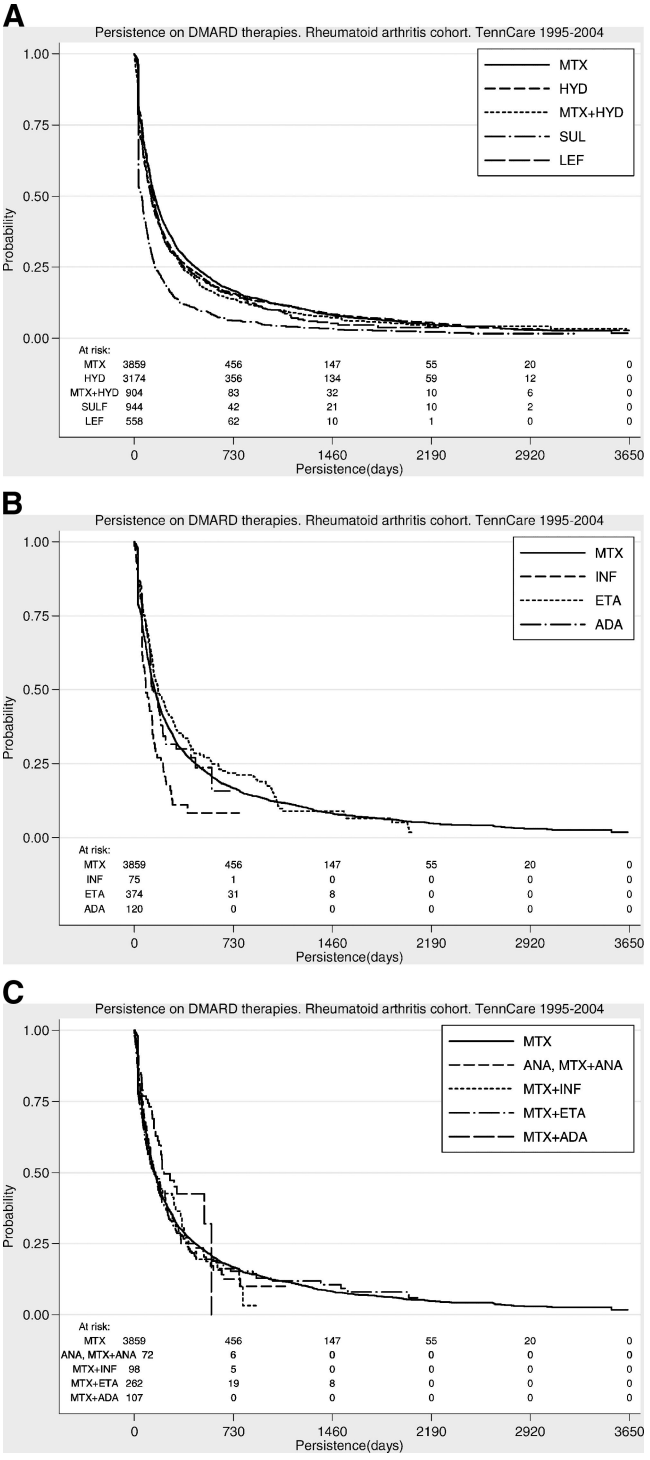

FIGURE 1. Overall persistence on DMARD therapies. Rheumatoid arthritis cohort. TennCare 1995–2004.

TABLE 2. Persistence on DMARD Therapies During New Episodes of Use

	No. New Episodes	Median Persistence (d)*	Events	Unadjusted HR	95% CI	Adjusted HR	95% CI	*P*
Overall persistence								
Methotrexate (MTX)	3859	150	3226	1.00	Reference	1.00	Reference	
Hydroxychloroquine (HYD)	3174	121	2709	1.04	(0.99–1.1)	1.03	(0.98–1.08)	0.319
Sulfasalazine	944	53	881	1.62	(1.5–1.76)	1.59	(1.47–1.72)	<0.001
Leflunomide	558	136	470	1.05	(0.96–1.15)	1.02	(0.93–1.11)	0.714
MTX + HYD	904	125	772	1.12	(1.03–1.21)	1.05	(0.97–1.14)	0.223
Infliximab	75	85	62	1.52	(1.21–1.89)	1.37	(1.09–1.73)	0.007
Etanercept	374	175	265	0.87	(0.78–0.98)	0.82	(0.73–0.92)	0.001
Adalimumab	120	134	71	0.96	(0.76–1.2)	0.85	(0.67–1.08)	0.188
MTX + infliximab	98	155	69	1.02	(0.82–1.28)	0.91	(0.73–1.15)	0.446
MTX + etanercept	262	147	203	1.06	(0.92–1.24)	1.01	(0.87–1.17)	0.884
MTX + adalimumab	107	219	46	0.68	(0.51–0.9)	0.63	(0.48–0.84)	0.002
Anakinra, MTX + Anak.	72	156	61	1.04	(0.82–1.3)	0.94	(0.75–1.18)	0.61
Persistence (time to stop filling medication)								
Methotrexate (MTX)	3859	232	2353	1.00	Reference	1.00	Reference	
Hydroxychloroquine (HYD)	3174	182	2048	1.06	(1–1.12)	1.01	(0.95–1.07)	0.845
Sulfasalazine	944	61	723	1.73	(1.59–1.88)	1.67	(1.53–1.82)	<0.001
Leflunomide	558	228	291	0.87	(0.78–0.98)	0.97	(0.86–1.09)	0.569
MTX + HYD	904		0	0.00		0.00		
Infliximab	75	231	28	0.90	(0.64–1.26)	0.97	(0.69–1.36)	0.845
Etanercept	374	688	135	0.60	(0.51–0.71)	0.67	(0.57–0.79)	<0.001
Adalimumab	120	211	44	0.79	(0.59–1.05)	0.86	(0.64–1.17)	0.333
MTX + infliximab	98		0	0.00		0.00		
MTX + etanercept	262		5	0.04	(0.01–0.09)	0.05	(0.02–0.11)	<0.001
MTX + adalimumab	107		0	0.00		0.00		
Anakinra, MTX + Anak.	72	783	22	0.50	(0.34–0.75)	0.56	(0.38–0.83)	0.004
Persistence (time to switch DMARD therapy)								
Methotrexate (MTX)	3859	1236	873	1.00	Reference	1.00	Reference	
Hydroxychloroquine (HYD)	3174	1456	661	0.97	(0.88–1.07)	1.02	(0.92–1.13)	0.724
Sulfasalazine	944	727	158	1.20	(1.01–1.41)	1.18	(1–1.39)	0.052
Leflunomide	558	560	179	1.53	(1.31–1.8)	1.12	(0.95–1.32)	0.191
MTX + HYD	904	125	772	4.19	(3.78–4.64)	2.84	(2.54–3.19)	<0.001
Infliximab	75	156	34	3.36	(2.39–4.74)	2.20	(1.58–3.07)	<0.001
Etanercept	374	515	130	1.61	(1.34–1.93)	1.10	(0.92–1.32)	0.288
Adalimumab	120		27	1.42	(0.97–2.09)	0.86	(0.58–1.26)	0.436
MTX + infliximab	98	155	69	3.94	(3.09–5.03)	2.28	(1.74–2.98)	<0.001
MTX + etanercept	262	159	198	3.88	(3.27–4.6)	2.37	(1.98–2.84)	<0.001
MTX + adalimumab	107	219	46	2.64	(1.97–3.54)	1.49	(1.1–2.02)	0.009
Anakinra, MTX + Anak.	72	280	39	2.53	(1.85–3.45)	1.58	(1.16–2.16)	0.004

*Blank cells indicate that less than 50% of episodes had outcomes of interest.

100 (51%) continued on etanercept. Finally, among 46 episodes of methotrexate + adalimumab that were switched to a different regimen, 16 (35%) and 24 (52%) continued on methotrexate and adalimumab, respectively.

Adherence to DMARD Therapies

The mean measurement of adherence (MPR) to DMARD therapies within episodes of use ranged from 0.64 for methotrexate + etanercept to 0.9 for infliximab alone. Compared with methotrexate and after adjustment for measured confounders, new users of sulfasalazine ($P = 0.014$), methotrexate + hydroxychloroquine ($P < 0.001$), methotrexate + infliximab ($P < 0.001$), methotrexate + etanercept ($P < 0.001$), methotrexate + adalimumab ($P = 0.001$), and anakinra alone or combined with methotrexate ($P = 0.008$), had lower mean adherence to treatment. New users of leflunomide ($P < 0.001$), infliximab ($P < 0.001$), etanercept ($P < 0.001$), and adalimumab ($P = 0.005$) alone had higher mean adherence than new users of methotrexate (Table 3). An alternative analysis, dichotomizing MPR values (defining adherence as MPR ≥ 0.8[19]) showed similar results.

TABLE 3. Adherence to DMARD Therapies During New Episodes of Use

Adherence Within Episodes	No. of New Episodes*	MPR (Mean)	Unadjusted Coefficient	95% CI	Adjusted Coefficient	95% CI	*P*
Methotrexate (MTX)	2933	0.80	1.00	Reference	1.00	Reference	
Hydroxychloroquine (HYD)	2206	0.79	−0.01	(−0.02 to 0)	0.00	(−0.01 to 0.01)	0.517
Sulfasalazine	491	0.77	−0.03	(−0.05 to 0.01)	−0.02	(−0.04 to 0)	0.014
Leflunomide	426	0.85	0.05	(0.03 to 0.07)	0.05	(0.04 to 0.07)	<0.001
MTX + HYD	691	0.66	−0.13	(−0.14 to −0.11)	−0.11	(−0.13 to −0.09)	<0.001
Infliximab	46	0.90	0.10	(0.05 to 0.15)	0.11	(0.06 to 0.16)	<0.001
Etanercept	308	0.83	0.03	(0.01 to 0.05)	0.04	(0.02 to 0.06)	<0.001
Adalimumab	96	0.85	0.05	(0.02 to 0.08)	0.04	(0.01 to 0.08)	0.005
MTX + infliximab	78	0.66	−0.12	(−0.18 to −0.07)	−0.12	(−0.17 to −0.07)	<0.001
MTX + etanercept	213	0.64	−0.12	(−0.15 to −0.09)	−0.11	(−0.14 to −0.08)	<0.001
MTX + adalimumab	92	0.72	−0.06	(−0.1 to −0.02)	−0.07	(−0.11 to −0.03)	0.001
Anakinra, MTX + Anak.	59	0.71	−0.08	(−0.14 to −0.02)	−0.08	(−0.13 to −0.02)	0.008

*Restricted to episodes with more than 1 prescription filled by DMARD.
MPR indicates medication possession ratio.

Concurrent Medications

Narcotics, corticosteroids, and NSAIDs were commonly prescribed during new episodes of DMARD use. The overall mean proportion of narcotic use was 0.35 and it ranged from 0.30 to 0.59 in new users of sulfasalazine and anakinra, or anakinra + methotrexate, respectively. Mean proportion of narcotic use was higher among new users of leflunomide compared with traditional DMARDs and even higher among new users of biologic therapies ($P < 0.001$). The mean proportion of corticosteroid use for all DMARDs was 0.31 and the mean proportion ranged from 0.26 in new users of hydroxychloroquine to 0.48 in new users of anakinra alone or combined with methotrexate. Corticosteroid use was higher among users of combined DMARD therapies, leflunomide, and adalimumab alone ($P < 0.001$). The mean proportion of NSAID use ranged from 0.32 in new users of infliximab alone to 0.44 in new users of adalimumab + methotrexate. However, NSAID use was similar among all DMARDs therapies ($P = 0.1875$) (Fig. 2).

DISCUSSION

Randomized clinical trials have consistently shown the efficacy of biologic DMARDs in controlling disease activity in patients with RA who were unresponsive to traditional treatment.[7–11] However, little is known about the effectiveness of these expensive medications in routine clinical practice.[41] Measurements of persistence and adherence can be used as surrogates for long-term effectiveness of therapies for RA. Using a large cohort of Medicaid enrollees with RA, we applied a new user design to compare measurements of persistence and adherence among users of traditional and biologic DMARDs. For this study, we specified criteria to measure the exposures and we defined maximum lengths of prescriptions and the length of time without a refill that constituted "stopping."[19] We avoided using artificial fixed lengths of follow-up (ie, 1 year) and we focused on new users because chronic (prevalent) users over-represent those with successful experiences and are not suitable for comparison.[32] Although we excluded patients with serious medical conditions from our analyses, their inclusion would further reduce the follow-up time available. Developing standard methodologies for these analyses need to be disease and drug-specific and sharing these methods may allow for better comparisons between and within populations.

Our study provides a comprehensive assessment of DMARD utilization in patients with RA in the community and it is not restricted to specialized care settings. Methotrexate, the reference DMARD, had relatively good overall persistence, as previously reported.[15,26] Consistent with other reports, we observed a lower persistence on sulfasalazine compared with our reference.[15,17,21] When compared with methotrexate, most biologic DMARDs had similar or better persistence. During the study period, infliximab was recommended for use with methotrexate to reduce the development of specific antibodies.[3,42] However, use of infliximab alone was observed in our cohort and has been described elsewhere.[43,44] In the present study, these episodes were short in duration and most of them likely represented initial treatment before the addition of methotrexate, as most episodes resulted in switching to methotrexate + infliximab. A previous report suggested better persistence in patients receiving either etanercept or infliximab combined with methotrexate compared with either biologic alone.[44] Our results suggest good persistence on etanercept alone or in combination with methotrexate. The use of etanercept alone is common[43,44]; it is efficacious in the treatment of RA[9] and its subcutaneous application might be an advantage compared with the intravenous infusion required for infliximab administration. However, physician prescribing patterns and insurance coverage could also influence these preferences.[45]

Adherence to DMARD therapy was similar among hydroxychloroquine and methotrexate users. Compared with adherence to methotrexate, adherence to sulfasalazine was lower, whereas adherence to leflunomide was higher. As previously noted, overall persistence was similar between episodes of leflunomide and methotrexate. This suggests that

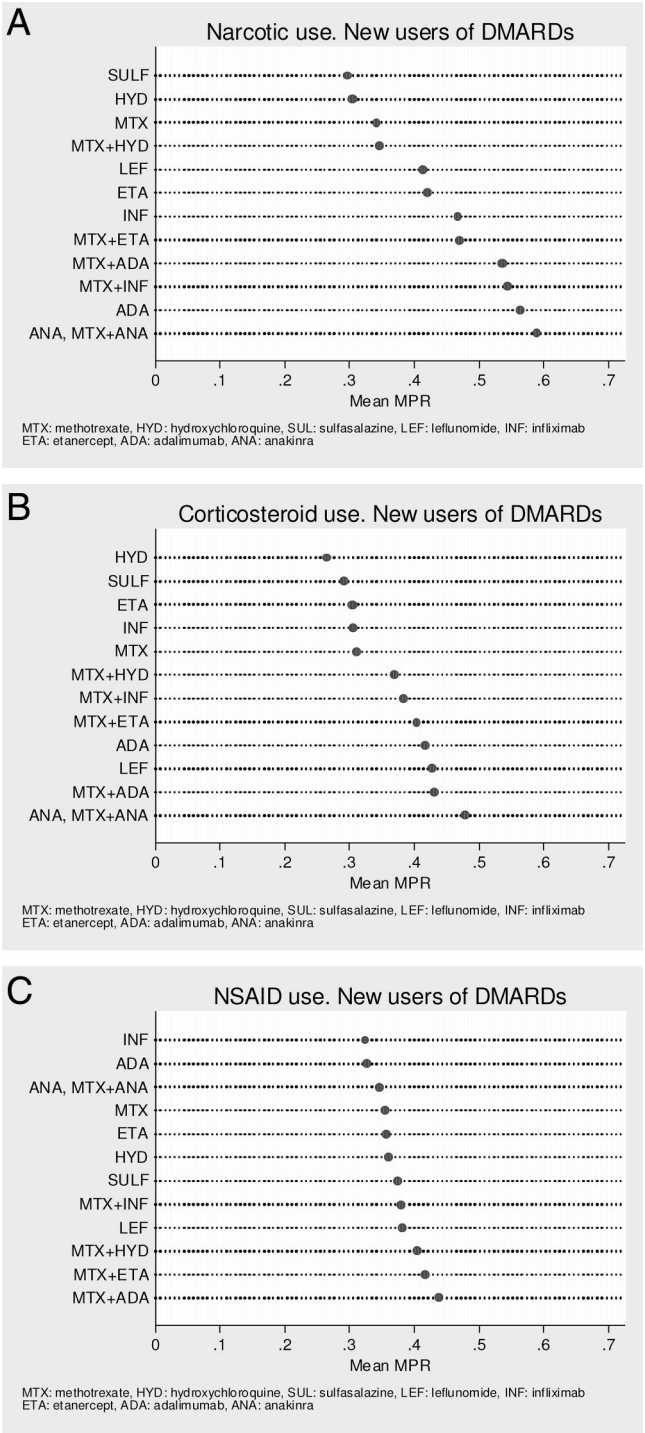

FIGURE 2. Concurrent medications within new episodes of DMARD use. Rheumatoid arthritis cohort. TennCare 1995–2004.

effectiveness is similar for these 2 medications[46] and that leflunomide is a useful alternative for those who experience adverse effects with methotrexate.[42] For biologic DMARDs, infliximab, etanercept, and adalimumab users were more likely to adhere to their treatment regimens compared with methotrexate users. As noted earlier, most episodes of use of infliximab alone were short and resulted in the addition of methotrexate.

Combined DMARD therapies accrued more days without medication available and consistently showed lower adherence compared with methotrexate. Most patients in our cohort were receiving medications for several comorbidities. Adding drugs for the treatment of RA, especially in combinations, likely increased the complexity of their treatments and might have contributed to the lower adherence observed in combined DMARD regimens.[18]

In our study, utilization of narcotics was common among RA patients receiving DMARDs. Users of biologic DMARDs, particularly recently introduced-biologics such as anakinra and adalimumab, tended to use more narcotics than users of traditional DMARDs, probably representing more severe disease and persistent pain despite DMARD treatment.[31] Corticosteroid use varied widely among DMARD therapies, whereas NSAID use was similar among different DMARD regimens. A previous examination of medication expenses in Medicaid programs reported an overall increase in utilization of narcotic analgesics from 1996 through 2002.[47] Further exploration of narcotic use in this population over time could provide insights into changing patterns of prescription and pain control treatments.

We performed a number of secondary analyses to evaluate the robustness of our findings. First, each patient could contribute more than 1 episode of use to the analysis and we repeated our analyses restricting the observations to the first episode of use per patient. Second, because nursing home residents may have no control over their medication use, the estimated persistence/adherence could be systematically inflated. All analyses were repeated excluding nursing home residents (0.63% of records). Third, we reanalyzed our data including hospitalization days and assuming medication consumption was uninterrupted during this time. Finally, because episodes that had only 1 prescription filled would tend to decrease our persistence estimates, we reanalyzed our data requiring at least 2 prescriptions filled for each episode of use. Results from these analyses did not differ materially from our original observations and our conclusions remained unaffected.

Despite the robustness of our results, their interpretation requires the consideration of several limitations. Patients with RA were identified through computerized diagnosis codes and not clinical criteria. However, our evaluation was restricted to patients who had compatible diagnoses and had started DMARD therapy. Furthermore, under TennCare regulations, prescription of biologic DMARDs needed to be endorsed by a rheumatologist before medications were dispensed.[48]

TennCare databases lack clinical information, such as disease activity or functional status, which might determine channeling of selected patients to specific DMARD therapies. In our population, new users of biologic DMARDs used ambulatory services and selected medications more frequently than users of traditional DMARDs, suggesting more severe or difficult to control disease activity. Moreover,

poorly controlled disease could result in additional comorbidities in these patients. Although our analyses accounted for a number of potential confounders (medical conditions, medications, and health care utilization) residual confounding cannot be ruled out. In this regard, disease duration has been important in some[49,50] but not in all studies,[51,52] and the role of disease severity is unclear.[51] Further, specific reasons for treatment discontinuation or poor adherence could not be evaluated using our resources. Other factors such as individual physician or patients preferences are important determinants for initiation or continuation on DMARD therapies,[41] but evaluating these factors would require different approaches.[53] Lastly, because TennCare enrollees represent a Medicaid population, these results may not generalize directly to other populations. Nevertheless, Medicaid covers a significant proportion of the US population that is typically excluded from premarketing studies and for whom limited information on medication effectiveness and safety is available.[13]

New therapeutic agents offer unprecedented benefits for RA patients; they might contribute to major improvements in both length and quality of life. We performed an assessment of patient adherence and persistence during new episodes of use of the most common DMARD therapies used for RA, including biologic DMARDs. Based on these measurements methotrexate stood out among the traditional DMARDs as relatively effective. Leflunomide and most biologic DMARDs had at least comparable persistence to methotrexate alone. Adherence was consistently lower for sulfasalazine and combined DMARD therapies when compared with methotrexate alone. The proper balance between these measurements of relative effectiveness will contribute to clinicians' ability to optimize treatment options for individual patients.

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