Predictors of Treatment Initiation with Tumor Necrosis Factor- α Inhibitors in Patients with Rheumatoid Arthritis

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ABSTRACT

BACKGROUND: Introduction of biologic disease-modifying antirheumatic drugs (DMARDs) has revolutionized treatment in patients with rheumatoid arthritis (RA). However, due to substantially higher costs of biologics compared with nonbiologics, patients with less insurance generosity may have difficulty affording these agents, which may lead to potential access disparities.

OBJECTIVE: To identify factors affecting treatment initiation with tumor necrosis factor (TNF)- α inhibitor biologics in patients with RA.

METHODS: Health insurance claims data derived from Truven's MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits (2007-2010) were used to conduct a retrospective cohort study. Two separate cohorts of RA patients were identified: (1) monotherapy nonbiologic DMARD users and (2) combination therapy nonbiologic DMARD users. The primary outcome was TNF- α inhibitor initiation 12 months following an index inpatient or outpatient RA visit during 2008-2009. Predictors were measured 12 months pre-index and grouped into predisposing, enabling, or need factors based on Andersen's Behavior Model. Predisposing variables included age, sex, and geographic location; enabling variables included insurance-related factors such as capitation, payer type, and insurance generosity, which was defined using cost-sharing information from prescriptions filled by the patients in the previous year; and need variables included disease-related factors such as severity of RA, use of pain control medications, and presence of other comorbidities. Hierarchical logistic regression models were used to derive estimates of the impact of individual predictors.

RESULTS: Initiation of TNF- α inhibitors was observed in 10.31% of the monotherapy nonbiologic DMARD users (1,922 of 18,641) and 13.09% of combination nonbiologic DMARD users (983 of 7,508). Among monotherapy nonbiologic DMARD users, initiation with TNF- α inhibitors was associated with the predisposing factors of age (OR=0.98, 95% CI=0.97-0.98 for each year increase) and geographic region (Midwest vs. South OR=0.83, 95% CI=0.73-0.93; Northeast vs. South OR=0.77, 95% CI=0.64-0.92; and West vs. South OR=0.86, 95% CI=0.74-0.99); enabling factors of visit to rheumatologists (1 visit vs. no visit OR=1.22, 95% CI=1.01-1.46), health insurance type (commercial vs. Medicare supplemental OR=0.79, 95% CI=0.66-0.95), and drug benefit generosity (above average vs. poor OR=1.16, 95% CI=1.01-1.34 and most generous vs. poor OR=1.21, 95% CI=1.05-1.40); and need factors of RA severity (OR=1.19, 95% CI=1.14-1.23 for each unit increase in a claims-based RA severity index [CIRAS]), pre-index pain reliever use (steroids OR=1.81, 95% CI=1.62-2.02; nonselective nonsteroidal anti-inflammatory drugs [NSAID] OR=1.17, 95% CI=1.05-1.31; COX-2 inhibitors OR=1.22, 95% CI=1.05-1.41), and comorbidities (OR=0.94, 95% CI=0.90-0.99 for each unit increase in a comorbidity index). Treatment initiation with TNF- α inhibitors among patients with combination therapy nonbiologic DMARDs use at baseline

was associated with age (OR=0.98, 95% CI=0.97-0.99 for each year increase) and region (Midwest vs. South OR=0.81, 95% CI=0.68-0.96). Stronger associations with some of the need factors were observed (CIRAS OR=1.28, 95% CI=1.21-1.35 for each unit increase, steroids use OR=2.05, 95% CI=1.73-2.42, and nonselective NSAID use OR=1.36, 95% CI=1.17-1.58) in these patients compared with the monotherapy nonbiologic DMARD users. However, unlike the monotherapy DMARD user group, the enabling factors of health insurance type and drug benefit generosity were not found to be associated with TNF- α inhibitor initiation among nonbiologic DMARD combination therapy users.

CONCLUSIONS: Potential disparities in the initiation of TNF- α inhibitors among RA patients on monotherapy DMARDs at baseline were noted among older patients, patients in certain geographic region of the United States, and patients with less generous prescription drug benefits. Although future research should examine the impact of these disparities on health outcomes, payers should be aware of the potential for undertreatment among these groups of RA patients when making formulary decisions.

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What is already known about this subject

- Biologic agents, indicated for the treatment of rheumatoid arthritis (RA) in patients who do not respond adequately to nonbiologics alone, are substantially more costly compared with nonbiologics.
- Prior studies from limited geographic regions of the United States suggest that certain patient characteristics, including lower income, minority race, and higher age, are negatively associated with biologic treatment in RA.

What this study adds

- This is the largest study based on U.S. commercial and Medicare population evaluating treatment predictors of tumor necrosis factor (TNF)- α inhibitor biologics conducted using a nationally representative sample of commercially insured RA patients.
- Among RA patients on monotherapy nonbiologics, insurance generosity was found to be a significant predictor of treatment initiation with TNF- α inhibitor biologics. However, among RA patients on combination therapy nonbiologics, the need for treatment, and not enabling characteristics such as insurance generosity, predicted treatment initiation with TNF- α inhibitor biologics. This observation demonstrates potential disparities related to patient cost sharing in the early stages of RA.

Rheumatoid arthritis (RA) is an autoimmune disease that affects approximately 1.3 million adults in the United States.¹ RA is associated with substantial morbidity and mortality.²⁻⁴ Disease-modifying antirheumatic drugs (DMARDs), which are generally classified into nonbiologics and biologics, form the mainstay of RA management. Nonbiologic DMARDs include agents, such as methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide, that halt disease progression by suppressing inflammation. In contrast, biologic DMARDs target specific components of the immune system, such as T cells, B cells, and cytokines (i.e., tumor necrosis factor (TNF)- α and interleukins), that play an important role in the pathogenesis of RA. Currently there are 10 biologics approved for the indication of RA: 5 TNF- α inhibitors (infliximab, etanercept, adalimumab, certolizumab, and golimumab), 2 interleukin inhibitors (tocilizumab and anakinra), a T-cell activation inhibitor (abatacept), a CD-20 activity blocker (rituximab), and a janus kinase inhibitor (tofacitinib). Among the available biologics, TNF- α inhibitors are the most commonly used agents, accounting for approximately 90% of the total biologic use.⁵ According to the American College of Rheumatology (ACR) recommendations, RA patients with low or moderate disease activity without features of poor prognosis should receive treatment with nonbiologic DMARDs, while RA patients with moderate-to-high disease severity with features of poor prognosis whose RA is not well controlled with nonbiologic DMARDs alone should receive treatment with biologic DMARDs.^{6,7}

Since all the biologics are only available as brands, they are substantially more costly than nonbiologic DMARDs. According to 1 estimate, the total direct costs for biologics are approximately 5-fold greater than nonbiologic DMARDs.² Given this cost, certain patient subgroups may have difficulty affording treatment, including patients with low income, less generous insurance coverage, and minority race. This is supported by studies that show lower biologic treatment initiation in RA patients with older age, lower income, and minority race.⁸⁻¹⁰ This disparity may lead to differences in such clinical outcomes as greater disease activity and lower remission rates in these patient subgroups.¹¹ Reduction in overall health services utilization costs through sustained remission in RA is well documented.¹² Therefore, from a payer's point of view, it is very important to understand and address potential disparities in the use of biologics among RA patients in order to control future health care costs.

Although previous studies have examined treatment disparities in particular subgroups,⁸⁻¹⁰ none has used a comprehensive model incorporating the variety of treatment determinants that might predict TNF- α inhibitor use. This study used Andersen's Behavioral Model (ABM) of health services use to examine TNF- α inhibitor use in a large cohort of commercially insured RA patients from the United States.¹³ ABM is a theoretical

model that uses a combination of factors grouped into predisposing, enabling, and need factors in order to predict the use of health care services. In addition, this study expanded on the current literature, which includes studies conducted in limited geographic regions of the United States,⁸⁻¹⁰ by evaluating factors influencing treatment initiation with TNF- α inhibitors in a nationally representative sample of RA patients. We exclusively focus on TNF- α inhibitor biologics because non-TNF biologics are generally reserved for a select group of patients who either fail to respond to a TNF- α inhibitor agent or are at an increased risk of adverse events from TNF- α inhibitors.⁶

Methods

Study Design and Data Source

A retrospective cohort study was designed to evaluate the predictors of TNF- α inhibitor treatment initiation in RA patients who were aged 18 years and older using data from Truven's MarketScan Commercial Claims And Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (COB) for the period between January 1, 2007, to December 31, 2010. These databases contain de-identified, person-specific health data including clinical utilization, expenditures, insurance enrollment/plan benefit, inpatient, outpatient, and prescription information. The CCAE contains health care data for nearly 40 million individuals, encompassing employees, their spouses, and their dependents. The COB contains the health care experiences of 3.8 million Medicare-eligible retirees with employer-sponsored Medicare supplemental plans.¹⁴ These patients have coordination of benefits, meaning that in addition to Medicare they have a private insurance plan paid for by their employers and therefore are not typical of the usual Medicare patient population. The Medicare supplemental dataset provided by Truven contains information on Medicare paid and supplemental insurance paid services.

Patient Identification and Exclusion Criteria

Diagnosis of RA was identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code of 714.0 on at least 2 outpatient or 1 inpatient insurance claims between January 1, 2008, and December 31, 2009. The date of the first claim was defined as the index date. In order to ensure continuous availability of health care data, we required patients to be continuously enrolled in their health plans 12 months pre-index (defined as the baseline period) and 12 months post-index (defined as the follow-up period). Combining diagnosis codes with DMARD prescription fills is known to result in a high positive predictive value (>85%) in identifying RA from administrative claims.¹⁵ Therefore, to improve the specificity of our RA identification algorithm, we further required these patients to have used at least 1 nonbiologic DMARD during the 12 months baseline period.

FIGURE 1 Study Design

DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

Given our focus on TNF- α inhibitor initiation, we excluded patients who used any biologic DMARDs during the 12-month baseline period. To ensure RA-specific TNF- α inhibitor initiation, we excluded patients having psoriatic arthritis or Crohn's disease (inflammatory conditions for which TNF- α inhibitor treatment is indicated). Further, to ensure that all the included patients were eligible to receive TNF- α inhibitors during follow-up, we excluded patients with a history of tuberculosis, which is a contraindication to TNF- α inhibitor use.

Eligible RA patients were followed for 12 months beginning from their index dates to examine initiation of TNF- α inhibitors (Figure 1). To contrast patient characteristics between nonbiologic DMARD users and TNF- α inhibitors users, patients who either did not fill any DMARD prescription or initiated treatment with non-TNF biologics prior to initiating TNF- α inhibitors were excluded during follow-up. Additionally, in order to compare RA patients at different stages of the disease separately, we created 2 separate cohorts based on nonbiologic DMARD use during the baseline period: (1) RA patients on monotherapy nonbiologic DMARDs in the baseline period—this cohort represented RA patients with mild-to-moderate disease activity without features of poor prognosis—and (2) RA patients on combination therapy nonbiologic DMARDs in the baseline period—this cohort represented RA patients with moderate-or-high disease activity with features of poor prognosis.

Measures

Predictors of biologic treatment initiation were measured during the 12-month baseline period in both cohorts and grouped according to the ABM for health services use.¹³ ABM posits a process of health care use in which predisposing factors influence the ability (measured through enabling factors) of a person to obtain health care that, when adding the need for treatment, predicts the use of health care services.

Predisposing Factors. Predisposing factors included the variables that may influence the likelihood of receiving health care services. Predisposing factors of age and sex from the ABM have successfully predicted some health care services use in RA patients in the past.¹⁶ Therefore, we hypothesized that patient demographic factors including age (as a continuous variable), gender (male/female), geographic location (Northeast, Midwest, West, and South), and urban/rural residence (as determined by metropolitan statistical areas [MSA]) may be able to explain the use of TNF- α inhibitors in this population.

Enabling Factors. Enabling factors included variables that may influence a patient's ability to secure health care services. Because of the high cost of TNF- α inhibitors, based on the ABM we hypothesized that RA patients with better means to secure health care may initiate these agents more frequently. We included the following factors as enabling variables to capture a patient's ability to secure health care services: visit to a rheumatologist as a categorical variable indicating no visit; 1 visit and more than 1 visit in the baseline period; the year of a patient's

index visit as a binary variable, 2008 or 2009; health plan type as a binary variable indicating capitated plan (included health maintenance organization or capitated point-of-service plans) or noncapitated plan (included basic major medical, comprehensive, exclusive and preferred provider organizations, noncapitated point of service, consumer-driven health plan, or high deductible health plan); type of insurance as a binary variable indicating either Medicare supplemental or commercial insurance; and drug benefit generosity. Drug benefit generosity was approximated by creating a “generosity index” using payment information from the prescriptions filled by patients in the 12-month baseline period.¹⁷ This index was calculated as a continuous variable in the range of 0-1 and was defined as the proportion of total drug costs paid by the patient out of pocket as copay or coinsurance. Based on this index, patients were classified into quartiles of drug benefit generosity to facilitate interpretation. The quartiles were termed as poor drug benefit generosity (fourth quartile, >33% cost shared by the patients), average drug benefit generosity (third quartile, 20%-33% cost shared by the patients), above average drug benefit generosity (second quartile, 10%-20% cost shared by the patients), and most generous drug benefit (lowest out-of-pocket costs, first quartile, <10% cost shared by the patients).

Need Factors. Need factors included health conditions of patients that necessitate the utilization of health services. Since TNF- α inhibitors are reserved for patients whose RA is not well controlled with nonbiologic DMARDs,⁶ we hypothesized that patients with more severe RA, as captured by the need variables in the ABM, may initiate TNF- α inhibitors more frequently. In this set, we included a continuous measure approximating disease severity (claims-based index of RA severity [CIRAS]) validated in a previous study.¹⁸ We also added indicators for baseline steroid use, nonsteroidal anti-inflammatory drug (NSAIDs) use, and COX-2 inhibitor use based on at least 1 dispensing of these agents during the baseline period. The comorbidity profile of patients, which was calculated as a continuous score based on the presence of 20 individual comorbid conditions, was also included in this set.¹⁹

The outcome variable of interest was initiation of a TNF- α inhibitor agent. We dichotomized TNF- α inhibitor initiation as present or absent based on pharmacy or medical claims indicating use of these agents during the 12-month period following the index date. The following TNF- α inhibitors were included in this study: adalimumab, certolizumab, etanercept, golimumab, and infliximab. The use of these agents was identified using both the National Drug Code (NDC) numbers from outpatient pharmacy files for filled prescriptions and J codes using outpatient services files for injectable agents administered at physician offices. The following NDCs were used: 00074937402, 00074379901, 00074379902, 00074433902, 00074433906, 00074433907, and 54868482200 for adalimumab; 50474070062 and 50474071079 for certolizumab; 54868478200, 58406042534, 58406042541, 58406045501,

58406045504, 58406043501, 58406043504, 58406044501, and 58406044504 for etanercept; 57894007001 and 57894007002 for golimumab; and 57894003001 for infliximab. The following J codes were used: J0135 for adalimumab, J0718 for certolizumab, J1438 for etanercept, and J1745 for infliximab.

Statistical Analyses

Descriptive statistics were used to summarize patient characteristics among TNF- α inhibitor initiators and nonbiologic DMARD users. For dichotomous and categorical variables, the results were presented as numbers and proportions. For continuous variables, the results were presented as mean ($\pm$ standard deviation). The patient factors were then compared between TNF- α inhibitor initiators and nonbiologic DMARD users with standardized differences.²⁰ Standardized differences were used to avoid statistically significant differences that have limited clinical importance between our 2 groups owing to the large sample size. A standardized difference of less than 10 suggests no correlation between the variable in question and the treatment group.

To understand the impact of various predictors on the initiation of TNF- α inhibitors while controlling for other variables, hierarchical logistic regression models were used in which the predictors were entered in 3 sets. The dependent variable in these models was a binary indicator for initiation of TNF- α inhibitors. The independent variables were grouped in 3 categories based on ABM: predisposing, enabling, and need variables. Predisposing variables were first included in the model followed by enabling variables and then need variables for both cohorts. Improvement in model fit was assessed using the Akaike information criterion (AIC) after addition of each set of variables. The goodness-of-fit of the logistic regression models were tested using Hosmer-Lemeshow tests. Linear equivalents of the logistic regression analyses were used to derive variance inflation factors (VIF), which were used to check for collinearity among the variables added to the model.²¹ All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Sensitivity Analyses

In order to evaluate the robustness of our findings, we undertook 2 sets of sensitivity analyses. First, Medicare and commercial enrollees may have different patient characteristics and coverage characteristics. Therefore, in order to evaluate whether our results are sensitive to pooling these patients and studying them as a single group, we fit logistic regression models predicting initiation of TNF- α inhibitors in Medicare and commercial enrollees separately in both cohorts. Second, certain TNF- α inhibitors that are administered at physician offices (most notably infliximab infusion) are likely to be covered under medical benefits, while other agents that are available as a self-injectable kit (e.g., etanercept) are more likely to be covered under pharmacy benefits. Therefore, to check whether our results apply to both physician-administered as

FIGURE 2 Study Sample Derivation

DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

well as prescription TNF- α inhibitors, we fit separate logistic regression models predicting initiation of both types of TNF- α inhibitors in both cohorts.

Results

Derivation of Study Cohorts

Figure 2 shows application of the inclusion and exclusion criteria for this study. We identified 44,709 RA patients who had at least 12 months pre-index and 12 months post-index continuous enrollment in their health plans. After excluding prevalent biologic users (15,246), patients ineligible for TNF- α inhibitor initiation (68), patients with comorbid inflammatory conditions (1,094), patients with no DMARD use during follow-up (1,599), and initiators of non-TNF-biologics (453), a total of 26,149 patients met all our inclusion criteria. These patients were then divided into 2 cohorts. Cohort 1, which included RA patients on monotherapy nonbiologic DMARDs in the baseline period, comprised 18,641 patients, and cohort 2, which included RA patients on combination therapy nonbiologic DMARDs, comprised 7,508 patients.

Patient Characteristics

A total of 1,922 patients (10.31%) among monotherapy nonbiologic users (cohort 1) and a total of 983 patients (13.09%) among combination therapy nonbiologic users (cohort 2) initiated treatment with a TNF- α inhibitor during the 12-month follow-up period. Table 1 compares the baseline characteristics of the TNF- α inhibitor initiators with patients who continued treatment with nonbiologic DMARDs during the follow-up period. Comparison of the predisposing variables suggested that the TNF- α inhibitor initiators were younger in both cohorts (mean age: 54 years vs. 62 years, standardized difference (SD) = 63.16 in cohort 1; 53 years vs. 60 years, SD = 57.18 in cohort 2). In both cohorts, patients in the South initiated TNF- α inhibitors more frequently, while patients in the Midwest initiated these agents less frequently. For the enabling variables, a lower proportion of the TNF- α inhibitor initiators had not visited a rheumatologist in the prior year compared with noninitiators only among monotherapy nonbiologic DMARD users (39.23% vs. 46.07%, SD = 13.87). The type of insurance was less frequently Medicare among the TNF- α inhibitor initiators in both cohorts

TABLE 1 Patient Characteristics of TNF- α Inhibitors Initiators and Noninitiators Stratified by Baseline DMARD Treatment, 2007-2010

Variable	Cohort 1: Monotherapy Nonbiologic DMARD Users at Baseline (n=18,641)			Cohort 2: Combination Therapy Nonbiologic Users at Baseline (n=7,508)		
	TNF- α Inhibitor Initiators (n = 1,922)	TNF- α Inhibitor Noninitiators (n = 16,719)	Standardized Difference ^a	TNF- α Inhibitor Initiators (n = 983)	TNF- α Inhibitor Noninitiators (n = 6,525)	Standardized Difference ^a
	n (%)	n (%)		n (%)	n (%)	
Predisposing factors						
Patient age, in years, mean (SD)	54 (12.4)	62 (13.5)	63.2	53 (11.9)	60 (12.6)	57.2
Female	1,477 (76.9)	12,456 (74.5)	5.5	783 (79.7)	4,998 (76.6)	7.4
Metropolitan statistical area	1,567 (81.6)	13,596 (81.3)	0.6	791 (80.5)	5,295 (81.2)	1.8
Region						
Northeast	158 (8.2)	1,882 (11.3)	10.2	69 (7.0)	552 (8.4)	5.4
North Central	507 (26.4)	5,372 (32.1)	12.7	278 (28.3)	2,326 (35.6)	15.9
South	959 (49.9)	6,509 (38.9)	22.2	450 (45.8)	2,328 (35.7)	20.7
West	298 (15.5)	2,956 (17.7)	5.8	186 (18.9)	1,319 (20.2)	3.3
Enabling factors						
Capitation						
Noncapitated health plan	1,618 (84.2)	14,101 (84.3)	0.4	806 (82.0)	5,404 (82.8)	2.2
Capitated health plan	304 (15.8)	2,618 (15.7)		177 (18.0)	1,121 (17.2)	
Visits to rheumatologists						
No visit in the prior year	754 (39.2)	7,703 (46.1)	13.9	398 (40.5)	2,833 (43.4)	5.9
At least 1 visit in the prior year	183 (9.5)	1,226 (7.3)	7.9	54 (5.5)	366 (5.6)	0.5
More than 1 visit in the prior year	985 (51.2)	7,790 (46.6)	9.3	531 (54.0)	3,326 (50.9)	6.1
Calendar year of the index visit						
2008	1,214 (63.2)	8,788 (52.6)	21.6	675 (68.7)	3,928 (60.2)	17.8
2009	708 (36.8)	7,931 (48.4)		301 (31.3)	2,597 (39.8)	
Payer type						
Commercial	1,647 (85.7)	10,508 (62.8)	54.1	847 (86.2)	4,362 (66.8)	46.8
Medicare	275 (14.3)	6,211 (37.1)		136 (13.8)	2,163 (33.1)	
Drug benefit generosity ^b						
Most generous	435 (22.7)	4,177 (25.1)	5.5	199 (20.2)	1,706 (26.2)	14.0
Better than average	472 (24.7)	4,096 (24.6)	0.1	263 (26.7)	1,686 (25.8)	2.0
Average	485 (25.3)	4,159 (25.0)	0.8	262 (26.6)	1,611 (24.7)	4.5
Below average	522 (27.3)	4,218 (25.3)	4.4	259 (26.3)	1,518 (23.3)	7.1
Need factors						
CIRAS, ^c mean (SD)	6.0 (1.9)	4.8 (1.9)	12.7	6.1 (1.9)	4.9 (1.8)	15.8
Comedications of interest						
COX-2 inhibitors	260 (13.5)	1,893 (11.3)	6.7	141 (14.3)	777 (11.9)	7.2
Nonsteroidal anti-inflammatory drugs	573 (29.8)	3,630 (21.7)	18.6	322 (32.8)	1,462 (22.4)	23.3
Steroids	1,391 (72.4)	9,668 (57.8)	30.9	774 (78.7)	4,067 (62.3)	36.6
Combined comorbidity score (CCS) ^d	0.3 (1.1)	0.5 (1.4)	12.2	0.4 (1.1)	0.5 (1.4)	10.6
Selected individual comorbid conditions from CCS ^d						
Congestive heart failure	70 (3.6)	1,035 (6.2)	11.8	27 (2.7)	420 (6.4)	17.7
Any tumor	65 (3.4)	1,254 (7.5)	18.2	39 (4.0)	469 (7.2)	14.1
Cardiac arrhythmias	89 (4.6)	1,391 (8.3)	15.0	46 (4.7)	502 (7.7)	12.5
Hypertension	687 (35.7)	6,976 (41.7)	12.3	323 (32.9)	2,644 (40.5)	15.9

^aA standardized difference of 10 (approximately equivalent to $P < 0.05$) indicates significant imbalance of a baseline covariate.

^bDrug benefit generosity was classified according to the quartiles of a calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were termed as poor drug benefit generosity (highest out-of-pocket costs, fourth quartile), average drug benefit generosity (third quartile), above average drug benefit generosity (second quartile), and most generous drug benefit (lowest out-of-pocket costs, first quartile).

^cCIRAS: Claims-based index of rheumatoid arthritis severity, which ranged from 0.6 to 10.7, with higher values indicating more severe rheumatoid arthritis.

^dA composite score indicating a patient's comorbidity burden after taking into account 20 individual conditions. The score ranged from -2 to 13 in our cohorts, with greater values indicating higher disease burden. From 20 individual conditions, only those with a standardized difference > 10 were shown.

DMARD=disease-modifying antirheumatic drug; SD=standard deviation; TNF=tumor necrosis factor.

TABLE 2 Multivariate Predictors of Treatment Initiation with TNF- α Inhibitors in RA Patients, 2007-2010

Variable	Predicting Treatment Initiation with TNF- α Inhibitors, OR (95% CI)	
	Cohort 1: Among Monotherapy Nonbiologic Users at Baseline	Cohort 2: Among Combination Nonbiologic Users at Baseline
Predisposing factors		
Patient age	0.98 (0.97-0.98)	0.98 (0.97-0.99)
Gender		
Female	1	1
Male	0.99 (0.88-1.11)	0.93 (0.78-1.11)
Metropolitan statistical area (MSA)		
Non-MSA	1	1
MSA	1.09 (0.96-1.24)	0.95 (0.79-1.13)
Region		
South	1	1
North Central	0.83 (0.73-0.94)	0.81 (0.68-0.96)
Northeast	0.77 (0.64-0.92)	0.84 (0.63-1.11)
West	0.86 (0.74-0.99)	0.94 (0.77-1.14)
Enabling factors		
Capitation		
Noncapitated health plan	1	1
Capitated plan	0.95 (0.83-1.09)	1.01 (0.84-1.22)
Visit to rheumatologist in the pre-index period		
No visit	1	1
At least 1 visit	1.21 (1.01-1.45)	0.87 (0.64-1.20)
More than 1 visit	0.95 (0.85-1.06)	0.75 (0.64-0.89)
Calendar year of index visit		
2008	1	1
2009	1.09 (0.97-1.22)	1.16 (0.98-1.38)
Insurance type		
Commercial	1	1
Medicare	0.75 (0.62-0.91)	0.90 (0.68-1.19)
Drug benefit generosity ^a		
Poor	1	1
Average	1.03 (0.90-1.18)	0.97 (0.80-1.18)
Better than average	1.16 (1.01-1.33)	1.01 (0.83-1.23)
Most generous	1.20 (1.04-1.39)	0.89 (0.72-1.10)
Need factors		
RA severity (CIRAS) ^b	1.19 (1.14-1.23)	1.28 (1.21-1.35)
Pain medication use		
No steroid use	1	1
Steroid use	1.80 (1.62-2.01)	2.04 (1.73-2.41)
No COX-2 inhibitor use	1	1
COX-2 inhibitor use	1.22 (1.06-1.41)	1.22 (0.99-1.50)
No NSAID use	1	1
NSAID use	1.17 (1.05-1.31)	1.36 (1.17-1.59)
Combined comorbidity score ^c	0.94 (0.90-0.98)	0.95 (0.90-1.01)

^aDrug benefit generosity was classified according to the quartiles of a calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were termed as poor drug benefit generosity (highest out-of-pocket costs, fourth quartile), average drug benefit generosity (third quartile), above average drug benefit generosity (second quartile), and most generous drug benefit (lowest out-of-pocket costs, first quartile).

^bCIRAS: Claims-based index of rheumatoid arthritis severity, which ranged from 0.6 to 10.7 with higher values indicating more severe rheumatoid arthritis.

^cA composite score indicating a patient's comorbidity burden after taking into account 20 individual conditions. The score ranged from -2 to 13 in our cohorts, with greater values indicating higher disease burden.

CI=confidence interval; NSAID=nonsteroidal anti-inflammatory drug; OR=odds ratio; TNF=tumor necrosis factor.

(14.31% vs. 37.15%, SD=54.13 in cohort 1; 13.84% vs. 33.15%, SD=46.79 in cohort 2). Among need variables, the severity of RA was found to be significantly greater among TNF- α inhibitors in both cohorts (mean CIRAS 5.96 vs. 4.70, SD=12.67 in cohort 1; 6.12 vs. 4.89, SD=15.85 in cohort 2). In both cohorts, a higher proportion of patients used NSAIDs during the baseline period compared with the noninitiator groups (29.81% vs. 21.71%, SD=18.60 in cohort 1; 32.76% vs. 22.41%, SD=23.32 in cohort 2). Steroid use was also more frequent in the TNF- α initiator groups in both cohorts (72.37% vs. 57.83%, SD=30.88 in cohort 1; 78.74% vs. 62.33%, SD=36.59 in cohort 2). Overall comorbidity burden was lower in the TNF- α inhibitor initiator group in both cohorts (mean score 0.30 vs. 0.46, SD=12.19 in cohort 1; 0.36 vs. 0.49, SD=10.62 in cohort 2).

Predictors of TNF- α Inhibitor Initiation

The results of our multivariate models that evaluated the influence of various predictors on treatment initiation with TNF- α inhibitors are presented in Table 2. The goodness-of-fit for both models was found to be adequate (P for Hosmer-Lemeshaw > 0.05), and no evidence for collinearity was observed for the variables added to the model (VIF < 5 for all the variables).

Among monotherapy nonbiologic users, the predisposing variables of patient age and geographic region were found to be significant predictors of TNF- α inhibitor initiation. Each year increase in age reduced the odds of TNF- α inhibitor initiation by 2% (odds ratio [OR]=0.98, 95% confidence interval [CI]=0.97-0.98). Patients in the Midwest, Northeast, and West regions had significantly lower likelihood of treatment initiation with TNF- α inhibitors compared with patients in the South (OR=0.83, 95% CI=0.73-0.93; OR=0.77, 95% CI=0.64-0.92; and OR=0.86, 95% CI=0.74-0.99, respectively). Of the enabling variables, having Medicare supplemental insurance had lower likelihood of TNF- α inhibitor treatment initiation compared with having commercial insurance (OR=0.75, 95% CI=0.62-0.91). On the other hand, patients who visited their rheumatologists once in the prior year had 21% higher odds of initiating a TNF- α inhibitor compared with those who did not visit their rheumatologists at all (OR=1.21, 95% CI=1.01-1.45). The drug benefit generosity variable also significantly predicted treatment initiation with a TNF- α inhibitor. Patients with better than average and the most generous drug benefit had 16% and 21% higher odds of initiating a TNF- α inhibitor compared with patients with poor drug benefits (OR=1.16, 95% CI=1.01-1.33; OR=1.20, 95% CI=1.04-1.39). All the need variables were found to have an association with TNF- α inhibitor initiation. With each unit increase in RA severity measure (CIRAS), the odds of TNF- α inhibitor initiation increased by 19% (OR=1.19, 95% CI=1.15-1.23). Previous use of steroids raised the odds of TNF- α inhibitor initiation by 80% (OR=1.80, 95% CI=1.62-2.01); previous use of NSAIDs raised the odds by 17% (OR=1.17, 95% CI=1.05-

1.31); and previous use of COX-2 inhibitors raised the odds by 22% (OR=1.22, 95% CI=1.06-1.41). Each unit decrease in the combined comorbidity score lowered the odds of TNF- α inhibitor initiation by 6% (OR=0.94, 95% CI=0.90-0.99). Addition of each sets of variables in the model improved the model fit for this cohort (AIC for the model with predisposing factors only=11,667; predisposing+enabling factors=11,640; and predisposing+enabling+need factors=11,386).

Some interesting contrasts were observed in the model predicting TNF- α inhibitor initiation among combination therapy nonbiologic users. Similar to monotherapy nonbiologic users, higher age was significantly associated inversely with TNF- α inhibitor initiation (OR=0.98, 95% CI=0.97-0.99), and patients in the Midwest had lower odds of initiating treatment with TNF- α inhibitors compared with patients in the South (OR=0.81, 95% CI=0.68-0.96). However, none of the enabling factors that predicted TNF- α inhibitor initiation in cohort 1 were found to be significantly associated with TNF- α inhibitor initiation in this cohort. Surprisingly, having visited a rheumatologist more than once in the prior year reduced the odds of TNF- α inhibitor initiation by 24%, compared with having no visit (OR=0.75, 95% CI=0.64-0.89). A stronger association between TNF- α inhibitor initiation and RA-related need factors, including CIRAS (OR=1.28, 95% CI=1.21-1.35), steroids use (OR=2.04, 95% CI=1.73-2.41), and NSAID use (OR=1.36, 95% CI=1.17-1.59) was observed in this cohort. Consistent with these observations, it was also noted that the addition of enabling variables to the model did not improve the model fit for this cohort, but addition of need variables improved the model fit (AIC for the model with predisposing factors only=5,559; predisposing+enabling factors=5,563; and predisposing+enabling+need factors=5,364).

Sensitivity Analyses Findings

In our first sensitivity analysis where we fit separate models predicting TNF- α inhibitors in commercial and Medicare enrollees, no noticeable differences in trends were observed compared with the main analysis in important explanatory variables including age, drug benefit generosity, and RA-related factors including CIRAS and steroid use (Appendix A, available in online article). However, since the estimates in Medicare were based on fewer TNF- α inhibitor initiations (275 in monotherapy and 136 in combination therapy) compared with estimates in commercial enrollees (1,647 in monotherapy and 847 in combination therapy), we observed estimates in Medicare enrollees with wider CIs. Additionally, certain factors, including gender, MSA, and visits to rheumatologists, were observed to have estimates that were numerically inconsistent (meaning on different sides of the null value of 1.0) between the 2 data sources. However, in all instances, the 95% CI for these estimates demonstrated considerable overlap between the 2 data sources.

In our second sensitivity analysis where we fit separate logistic regression models predicting initiation of physician-admin-

istered and prescription-filled TNF- α inhibitors, the majority of the findings were similar (Appendix B, available in online article). However, the drug benefit generosity variable was a stronger predictor of TNF- α inhibitors filled at a pharmacy, while it did not predict the initiation of physician-administered TNF- α inhibitors in the monotherapy cohort, unlike our main analysis.

Discussion

Findings from the current study provide insights into real-world treatment initiation patterns of TNF- α inhibitors in patients with RA. One of the purposes of our study was to examine potential disparities in treatment using a well-defined conceptual model. As suggested by the ABM, under an equitable health care system, the use of health care services would primarily be driven by need factors. However, we found significant variation in TNF- α inhibitor initiation across patients, with predisposing factors—including age and geographic region—as well as enabling factors—including visit to rheumatologists, drug benefit generosity, and insurance type—playing a role in treatment initiation with TNF- α inhibitors. This is potentially suggestive of inequitable access among RA patients. A recent investigation observed that close to 50% of RA patients did not receive care consistent with the 2008 ACR guidelines.²² Our study identifies some of the potential factors that may be contributing to this worrisome trend.

In order to better characterize factors influencing treatment initiation with TNF- α inhibitors, we separately evaluated the effects of various sets of predictors in 2 cohorts of patients with different stages of RA, as suggested by either monotherapy or combination therapy nonbiologic use during the baseline period. We observed that in the cohort of monotherapy nonbiologic users, patients with certain demographics (younger age or residence in the South) and with better means to secure health care (care of rheumatologists or health plans with a higher drug benefit generosity) had higher odds of initiating treatment with TNF- α inhibitors. These results suggest that during the early stages of the disease, potential disparities in access to the costly TNF- α inhibitors may exist. Delay in initiation of timely TNF- α inhibitors may lead to higher probability of radiographic progression and hence reduced quality of life among these patients.²³ Prior research has also demonstrated that RA patients with multiple failed nonbiologic DMARDs prior to initiating a TNF- α inhibitor have lower odds for treatment response with TNF- α inhibitors.²⁴ This further emphasizes the importance of timely initiation of TNF- α inhibitors in RA patients. Because of the substantially higher cost of biologics, there is a potential for inequitable access in the use of these agents among RA patients. The coverage of biologics under a higher or specialty formulary tier of pharmacy benefits has become increasingly common.²⁵ Research suggests that this practice has substantially increased the out-of-pocket costs for biologics.^{25,26} Greater patient cost sharing has been known

to delay or reduce the odds of initiation of treatments in various disease conditions,²⁷ including RA.²⁸ In the current study, we reported findings in line with these observations among RA patients who were on monotherapy nonbiologic DMARDs at baseline. Reduction in patient cost sharing may represent a potential strategy for payers to increase the odds of timely biologic initiation.

Among RA patients with moderate-or-high disease activity with features of poor prognosis (as approximated by combination nonbiologic DMARDs use at baseline in cohort 2), we observed that need factors mostly explained the initiation of TNF- α inhibitors, and enabling factors, such as insurance generosity and insurance type, played little role. This finding suggests less potential for disparity in TNF- α inhibitor treatment use among commercially insured patients with higher need for treatment. Although our finding of having visited a rheumatologist more than once in the prior year resulting in lower odds of TNF- α inhibitor initiation compared with no visit in this cohort may seem counterintuitive at first glance, we postulate that this may reflect improved RA management under the constant care of a rheumatologist, which may in turn result in lower need for TNF- α inhibitor initiation in these patients.

It was interesting to note that TNF- α inhibitor initiators were younger than patients not initiating these treatments. This is consistent with prior studies that evaluated initiation of biologics specifically,⁸⁻¹⁰ as well as several studies that examined the use of DMARDs as a class.²⁹⁻³¹ This inverse association between age and TNF- α inhibitor initiation may be attributed to several factors. It is likely that older patients may be at a higher risk for adverse events of TNF- α inhibitors, owing to a higher burden of comorbid conditions and frailty. Although the literature suggests similar effectiveness of TNF- α inhibitors across different age groups,^{32,33} our finding of their differential use based on age is concerning because it may reflect less aggressive RA management and possibly uncontrolled RA in older patients. Another factor leading to less aggressive treatment in older RA patients may be physician preference.³⁴ We also observed that patients in the South were more likely to initiate treatment with TNF- α inhibitors. Ours is the first study to document regional variations in the initiation of treatment with TNF- α inhibitors. The regional variation we observed persisted after controlling for other predisposing, enabling, and need factors. Prior research has documented substantial regional variation in prescription medication utilization among Medicare Part D enrollees in the United States, and some of the factors contributing to the geographic variation may include prescriber practice styles, prescriber awareness, and patient preferences.³⁵

The significant association of higher RA severity score and pre-index pain medication use with TNF- α inhibitor treatment initiation is an expected finding because these need variables represent high RA activity. We also observed strong trends towards lower likelihood of TNF- α inhibitor initiation among

patients with higher combined comorbidity scores. This finding may reflect the fact that TNF- α inhibitors are contraindicated in a variety of comorbid conditions, including congestive heart failure, multiple sclerosis, and a variety of infections, while nonbiologic DMARDs are not.³⁶ Therefore, it is possible that physicians may avoid TNF- α inhibitor treatment in RA patients with a higher burden of comorbidities.

Our study has several unique strengths. First, this is the largest study of its kind conducted in RA patients from all over the United States, who are enrolled in commercial or Medicare supplemental insurance, that provides estimates on the influence of population characteristics on TNF- α inhibitor treatment initiation. Second, because of the availability of diagnoses for various comorbid conditions within the claims, we were able to exclude patients with contraindications and risk-adjust our estimates based on the presence of various comorbidities. Third, we carefully constructed 2 cohorts of RA patients according to their disease progression based on their baseline DMARD use and predicted initiation of TNF- α inhibitors separately in each cohort. This approach ensured the inclusion of homogenous groups of patients in each cohort and provided insights into factors that were differentially associated with TNF- α inhibitor initiation in each of the cohorts. Finally, we conducted extensive sensitivity analyses to evaluate the robustness of our findings.

Limitations

We also acknowledge several limitations of this study. As with any other study using administrative claims, we were not able to validate the diagnoses of the disease condition (RA). To address this limitation, we used nonbiologic DMARD prescriptions in pharmacy claims along with ICD-9-CM codes on inpatient or outpatient visit to identify RA. Combining DMARD claims with diagnosis codes has been shown to result in a high positive predictive value (86%) for identifying RA in administrative claims in a prior validation study.¹⁵ Further, the administrative claims contain very limited information on clinical conditions of RA patients, such as disease activity and swollen joint count. Therefore, we were not able to capture the exact severity of RA in patients in our cohorts. However, as a proxy, we used the validated claims-based index for getting an approximation of RA severity.¹⁸ Next, because of the unavailability of information on important patient factors, including race, education, income, and family medical cost burden, our study cannot explain potential disparities in TNF- α inhibitor initiation owing to these factors. Additionally, claims data may have incomplete information on certain variables. For instance, provider type is coded as “unknown” on some physician visits. This may have artificially inflated the number with zero visits to rheumatologists and deflated the number with 1 and more than 1 visit. As a result, the absolute percentage reported in Table 1 may not represent a typical care pattern by

rheumatologists of RA patients with commercial or Medicare supplemental insurance. However, we do not expect the amount of missing information to be related to the initiation of TNF-inhibitors. Therefore, we postulate that our effect estimates in Table 2 are not systematically biased due to this problem. Next, an important factor leading to TNF- α inhibitor initiation may be physician preference, independent of patient need for treatment.³⁷ Since we did not have information about this important variable in our data, our study cannot explain potential variability related to physician preferences. Finally, the insurance claims data only represent employed individuals and their dependents, and the Medicare supplemental data only represent retirees whose insurance are paid by their employers, which somewhat limits the generalizability of our study.

Conclusions

Potential disparities in the initiation of TNF- α inhibitors among RA patients on monotherapy DMARDs at baseline were noted among older patients, patients in certain geographic regions of the United States, and patients with less generous prescription drug benefits among commercial and Medicare supplemental participants. Although future research should examine the impact of these disparities on health outcomes, payers should be aware of the potential for undertreatment among these groups of RA patients when making formulary decisions. Among patients on combination therapy DMARDs, little impact of enabling factors, including drug benefit generosity and data type on the initiation of TNF- α inhibitors, was observed. Future research using data that have detailed information on drug benefit structure of health plans of the patients should be considered to confirm our findings.

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DISCLOSURES

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Study concept and design were primarily contributed by Desai and Farley, with assistance from Rao, Hansen, Fang, and Maciejewski. Desai and Farley collected the data, which were interpreted by Maciejewski, Hansen, and Desai, assisted by Rao, Fang, and Farley. The manuscript was written by Desai, Fang, Rao, and Hansen, assisted by Farley and Maciejewski, and revised by Desai, Rao, Hansen, and Fang, assisted by Maciejewski and Farley.

REFERENCES

- Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008;58(1):15-25.
- Michaud K, Messer J, Choi HK, Wolfe F. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. *Arthritis Rheum*. 2003;48(10):2750-62.
- Pugner KM, Scott DI, Holmes JW, Hieke K. The costs of rheumatoid arthritis: an international long-term view. *Semin Arthritis Rheum*. 2000;29(5):305-20.
- Cooper NJ. Economic burden of rheumatoid arthritis: a systematic review. *Rheumatology (Oxford)*. 2000;39(1):28-33.
- McBride S, Sarsour K, White LA, Nelson DR, Chawla AJ, Johnston JA. Biologic disease-modifying drug treatment patterns and associated costs for patients with rheumatoid Arthritis. *J Rheumatol*. 2011;38(10):2141-49.
- Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(5):625-39.
- Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis*. 2010;69(6):976-86.
- Yelin E, Tonner C, Kim SC, et al. Sociodemographic, disease, health system, and contextual factors affecting the initiation of biologic agents in rheumatoid arthritis: a longitudinal study. *Arthritis Care Res (Hoboken)*. 2014;66(7):980-89.
- Chu LH, Portugal C, Kawatkar AA, Stohl W, Nichol MB. Racial/ethnic differences in the use of biologic disease-modifying antirheumatic drugs among California Medicaid rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)*. 2013;65(2):299-303.
- DeWitt EM, Lin L, Glick HA, Anstrom KJ, Schulman KA, Reed SD. Pattern and predictors of the initiation of biologic agents for the treatment of rheumatoid arthritis in the United States: an analysis using a large observational data bank. *Clin Ther*. 2009;31(8):1871-80.
- Greenberg JD, Spruill TM, Shan Y, et al. Racial and ethnic disparities in disease activity in patients with rheumatoid arthritis. *Am J Med*. 2013;126(12):1089-98.
- Barnabe C, Thanh N, Ohinmaa A, et al. Healthcare service utilisation costs are reduced when rheumatoid arthritis patients achieve sustained remission. *Ann Rheum Dis*. 2013;72(10):1664-68.
- Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *J Health Soc Behav*. 1995;36(1):1-10.
- Danielson E. Health research data for the real world: the MarketScan databases. White paper. January 2014. Available at: http://truvenhealth.com/Portals/0/Users/031/31/31/PH_13434%200314_MarketScan_WP_web.pdf. Accessed September 30, 2014.

15. Kim SY, Servi A, Polinski JM, et al. Validation of rheumatoid arthritis diagnoses in health care utilization data. *Arthritis Res Ther*. 2011;13(1):R32.
16. Jacobi CE, Triemstra M, Rupp I, Dinant HJ, Van Den Bos GA. Health care utilization among rheumatoid arthritis patients referred to a rheumatology center: unequal needs, unequal care? *Arthritis Rheum*. 2001;45(4):324-30.
17. Artz MB, Hadsall RS, Schondelmeyer SW. Impact of generosity level of outpatient prescription drug coverage on prescription drug events and expenditure among older persons. *Am J Public Health*. 2002;92(8):1257-63.
18. Ting G, Schneeweiss S, Scranton R, et al. Development of a health care utilisation data-based index for rheumatoid arthritis severity: a preliminary study. *Arthritis Res Ther*. 2008;10(4):R95.
19. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64(7):749-59.
20. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009;38(6):1228-34.
21. Allison PD. *Logistic Regression Using the SAS System: Theory and Application*. Wiley-SAS Publishing; 2001.
22. Harrold LR, Harrington JT, Curtis JR, et al. Prescribing practices in a U.S. cohort of rheumatoid arthritis patients before and after publication of the American College of Rheumatology treatment recommendations. *Arthritis Rheum*. 2012;64(3):630-38.
23. Keystone EC, Breedveld FC, van der Heijde D, et al. Long-term effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension. *J Rheumatol*. 2014;41(1):5-14.
24. Hyrich KL, Watson KD, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF- α therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)*. 2006;45(12):1558-65.
25. Goldman DP, Joyce GF, Lawless G, Crown WH, Willey V. Benefit design and specialty drug use. *Health Aff (Millwood)*. 2006;25(5):1319-31.
26. Polinski JM, Mohr PE, Johnson L. Impact of Medicare Part D on access to and cost sharing for specialty biologic medications for beneficiaries with rheumatoid arthritis. *Arthritis Rheum*. 2009;61(6):745-54.
27. Solomon MD, Goldman DP, Joyce GF, Escarce JJ. Cost sharing and the initiation of drug therapy for the chronically ill. *Arch Intern Med*. 2009;169(8):740-48.
28. Karaca-Mandic P, Joyce GF, Goldman DP, Laouri M. Cost sharing, family health care burden, and the use of specialty drugs for rheumatoid arthritis. *Health Serv Res*. 2010;45(5 Pt 1):1227-50.
29. Bonafede MM, Fox KM, Johnson BH, Watson C, Gandra SR. Factors associated with the initiation of disease-modifying antirheumatic drugs in newly diagnosed rheumatoid arthritis: a retrospective claims database study. *Clin Ther*. 2012;34(2):457-67.
30. Desai R, Agarwal S, Aparasu R. Drug utilization trends for arthritis and other rheumatic conditions and impact of patients' age on treatment choice. *N C Med J*. 2011;72(6):432-38.
31. Tutuncu Z, Reed G, Kremer J, Kavanaugh A. Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? *Ann Rheum Dis*. 2006;65(9):1226-29.
32. Bathon JM, Fleischmann RM, Van der Heijde D, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. *J Rheumatol*. 2006;33(2):234-43.
33. Genevay S, Finckh A, Ciurea A, Chamot AM, Kyburz D, Gabay C. Tolerance and effectiveness of anti-tumor necrosis factor alpha therapies in elderly patients with rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum*. 2007;57(4):679-85.
34. Fraenkel L, Rabidou N, Dhar R. Are rheumatologists' treatment decisions influenced by patients' age? *Rheumatology*. 2006;45(12):1555-57.
35. Munson J, Morden N, Goodman D, Valle N, Wennberg J. The Dartmouth atlas of medicare prescription drug use. The Dartmouth Institute for Health Policy & Clinical Practice. October 15, 2013. Available at: http://www.dartmouthatlas.org/downloads/reports/Prescription_Drug_Atlas_101513.pdf. Accessed September 22, 2014.
36. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 2008;59(6):762-84.
37. Curtis JR, Chen L, Harrold LR, Narongroeknawin P, Reed G, Solomon DH. Physician preference motivates the use of anti-tumor necrosis factor therapy independent of clinical disease activity. *Arthritis Care Res (Hoboken)*. 2010;62(1):101-07.

APPENDIX A Multivariate Predictors of Treatment Initiation with TNF- α Inhibitors in RA Patients by Data Source, 2007-2010

Variables	Medicare Data, OR (95% CI)		Commercial Data, OR (95% CI)	
	Among Monotherapy Nonbiologic Users at Baseline	Among Combination Therapy Nonbiologic Users at Baseline	Among Monotherapy Nonbiologic Users at Baseline	Among Combination Therapy Nonbiologic Users at Baseline
Predisposing factors				
Patient age	0.94 (0.92-0.96)	0.97 (0.94-1.00)	0.98 (0.97-0.99)	0.99 (0.98-0.99)
Gender				
Female	1	1	1	1
Male	0.79 (0.59-1.04)	0.78 (0.51-1.17)	1.03 (0.91-1.17)	0.96 (0.80-1.17)
Metropolitan statistical area (MSA)				
Non-MSA	1	1	1	1
MSA	0.84 (0.61-1.15)	0.63 (0.41-0.98)	1.15 (1.00-1.32)	1.02 (0.83-1.24)
Region				
South	1	1	1	1
North Central	0.56 (0.41-0.76)	0.70 (0.46-1.08)	0.88 (0.77-1.01)	0.84 (0.70-1.02)
Northeast	0.70 (0.46-1.06)	1.12 (0.61-2.06)	0.78 (0.63-0.96)	0.76 (0.55-1.04)
West	0.98 (0.69-1.38)	0.95 (0.56-1.61)	0.82 (0.70-0.96)	0.94 (0.76-1.18)
Enabling factors				
Capitation				
Noncapitated health plan	1	1	1	1
Capitated plan	0.84 (0.56-1.25)	0.77 (0.43-1.37)	0.97 (0.84-1.13)	1.08 (0.88-1.32)
Visit to rheumatologist in the pre-index period				
No visit	1	1	1	1
At least 1 visit	1.84 (1.15-2.93)	1.48 (0.67-3.26)	1.13 (0.93-1.37)	0.81 (0.57-1.14)
More than 1 visit	1.25 (0.95-1.66)	1.07 (0.72-1.58)	0.91 (0.81-1.03)	0.72 (0.60-0.86)
Calendar year of the index visit				
2008	1	1	1	1
2009	0.88 (0.59-1.13)	0.87 (0.56-1.35)	1.05 (0.92-1.29)	1.11 (0.88-1.45)
Drug benefit generosity ^a				
Poor	1	1	1	1
Average	1.07 (0.71-1.61)	0.93 (0.50-1.73)	1.02 (0.88-1.18)	0.98 (0.80-1.21)
Better than average	1.31 (0.88-1.94)	1.07 (0.59-1.94)	1.11 (0.96-1.29)	1.00 (0.81-1.23)
Most generous	1.37 (0.93-2.02)	1.38 (0.79-2.42)	1.16 (0.99-1.36)	0.78 (0.62-0.99)
Need factors				
RA factors				
CIRAS ^b	1.17 (1.05-1.30)	1.14 (0.97-1.33)	1.19 (1.15-1.24)	1.31 (1.24-1.39)
No steroid use	1	1	1	1
Steroid use	1.66 (1.26-2.19)	2.24 (1.44-3.48)	1.82 (1.62-2.05)	2.00 (1.67-2.40)
No coxib use	1	1	1	1
Coxib use	0.98 (0.68-1.41)	1.73 (1.09-2.77)	1.27 (1.08-1.49)	1.12 (0.89-1.41)
No NSAID use	1	1	1	1
NSAID use	0.95 (0.68-1.33)	1.26 (0.80-1.99)	1.19 (1.06-1.34)	1.37 (1.17-1.62)
Combined comorbidity score ^c	0.91 (0.84-0.99)	0.95 (0.85-1.06)	0.96 (0.92-1.01)	0.96 (0.90-1.03)

^aDrug benefit generosity was classified according to the quartiles of a calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were termed as poor drug benefit generosity (highest out-of-pocket costs, fourth quartile), average drug benefit generosity (third quartile), above average drug benefit generosity (second quartile), and most generous drug benefit (lowest out-of-pocket costs, first quartile).

^bCIRAS: Claims-based index of rheumatoid arthritis severity, which ranged from 0.6 to 10.7 with higher values indicating more severe rheumatoid arthritis.

^cA composite score indicating a patient's comorbidity burden after taking into account 20 individual conditions. The score ranged from -2 to 13 in our cohorts, with greater values indicating higher disease burden.

CI=confidence interval; NSAID=nonsteroidal anti-inflammatory drug; OR=odds ratio; RA=rheumatoid arthritis; TNF=tumor necrosis factor.

APPENDIX B Multivariate Predictors of Treatment Initiation with TNF- α Inhibitors in RA Patients by the Source of Treatment Receipt, 2007-2010

Variables	Pharmacy-Filled TNF- α Inhibitors, OR (95% CI)		Physician-Administered TNF- α Inhibitors, OR (95% CI)	
	Among Monotherapy Nonbiologic Users at Baseline	Among Combination Therapy Nonbiologic Users at Baseline	Among Monotherapy Nonbiologic Users at Baseline	Among Combination Therapy Nonbiologic Users at Baseline
Predisposing factors				
Patient age	0.97 (0.97-0.98)	0.98 (0.97-0.99)	1.00 (0.98-1.01)	0.98 (0.97-1.00)
Gender				
Female	1	1	1	1
Male	1.02 (0.9-1.16)	0.93 (0.77-1.13)	0.91 (0.72-1.15)	0.96 (0.68-1.37)
Metropolitan statistical area (MSA)				
Non-MSA	1	1	1	1
MSA	1.04 (0.91-1.2)	0.92 (0.75-1.11)	1.28 (0.98-1.68)	1.08 (0.73-1.60)
Region				
South	1	1	1	1
North Central	0.92 (0.81-1.06)	0.85 (0.71-1.03)	0.58 (0.45-0.74)	0.69 (0.48-0.98)
Northeast	0.84 (0.68-1.03)	0.84 (0.62-1.15)	0.58 (0.40-0.84)	0.81 (0.46-1.42)
West	0.94 (0.8-1.11)	1.00 (0.80-1.25)	0.62 (0.46-0.83)	0.77 (0.50-1.18)
Enabling factors				
Capitation				
Noncapitated health plan	1	1	1	1
Capitated plan	0.92 (0.79-1.07)	0.90 (0.73-1.11)	1.12 (0.86-1.46)	1.55 (1.09-2.20)
Visit to rheumatologist in the pre-index period				
No visit	1	1	1	1
At least 1 visit	1.13 (0.92-1.39)	0.86 (0.61-1.22)	1.44 (1.02-2.02)	0.92 (0.46-1.81)
More than 1 visit	0.96 (0.85-1.09)	0.72 (0.60-0.86)	0.90 (0.71-1.13)	0.91 (0.65-1.27)
Calendar year of the index visit				
2008	1	1	1	1
2009	1.13 (1.00-1.28)	1.15 (0.95-1.39)	0.95 (0.75-1.20)	1.24 (0.87-1.75)
Data source				
Commercial	1	1	1	1
Medicare	0.57 (0.45-0.72)	0.75 (0.54-1.03)	1.31 (0.90-1.89)	1.53 (0.89-2.65)
Drug benefit generosity ^a				
Poor	1	1	1	1
Average	1.04 (0.89-1.21)	0.93 (0.75-1.15)	1.01 (0.77-1.32)	1.20 (0.80-1.78)
Better than average	1.18 (1.01-1.38)	1.02 (0.83-1.27)	1.06 (0.80-1.40)	0.99 (0.65-1.50)
Most generous	1.26 (1.07-1.47)	0.89 (0.71-1.12)	1.04 (0.78-1.38)	0.90 (0.58-1.41)
Need factors				
RA factors				
CIRAS ^b	1.19 (1.14-1.24)	1.29 (1.21-1.37)	1.19 (1.11-1.28)	1.25 (1.11-1.39)
No steroid use	1	1	1	1
Steroid use	1.74 (1.54-1.97)	2.05 (1.70-2.46)	2.06 (1.64-2.59)	2.04 (1.43-2.92)
No coxib use	1	1	1	1
Coxib use	1.24 (1.06-1.47)	1.09 (0.86-1.38)	1.17 (0.88-1.57)	1.76 (1.20-2.58)
No NSAID use	1	1	1	1
NSAID use	1.19 (1.05-1.34)	1.33 (1.12-1.57)	1.12 (0.90-1.40)	1.58 (1.15-2.16)
Combined comorbidity score ^c	0.96 (0.91-1.00)	0.96 (0.90-1.02)	0.90 (0.83-0.98)	0.94 (0.83-1.05)

^aDrug benefit generosity was classified according to the quartiles of a calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were termed as poor drug benefit generosity (highest out-of-pocket costs, fourth quartile), average drug benefit generosity (third quartile), above average drug benefit generosity (second quartile), and most generous drug benefit (lowest out-of-pocket costs, first quartile).

^bCIRAS: Claims-based index of rheumatoid arthritis severity, which ranged from 0.6 to 10.7 with higher values indicating more severe rheumatoid arthritis.

^cA composite score indicating a patient's comorbidity burden after taking into account 20 individual conditions. The score ranged from -2 to 13 in our cohorts, with greater values indicating higher disease burden.

CI=confidence interval; NSAID=nonsteroidal anti-inflammatory drug; OR=odds ratio; RA=rheumatoid arthritis; TNF=tumor necrosis factor.