Risk of Significant Infection in Rheumatoid Arthritis Patients Switching Anti-Tumor Necrosis Factor-α Drugs

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Objectives: To describe rates of first significant infection of rheumatoid arthritis patients who switch between anti-tumor necrosis factor (aTNF) drugs.

Methods: Subjects with rheumatoid arthritis who received only aTNF drugs were observed in an insurance claims database from January 2001 to December 2007. Nonswitchers (NS) remained on one aTNF throughout the study period (date of the first aTNF claim was the index date); switchers (S) received at least one other aTNF (claim date for the 2nd agent was the index date). Significant infections included those that required intravenous antibiotics or hospitalization. Two attributable risk periods were used: (1) an infection occurring ≤90 days following a claim for an aTNF (90-day) and (2) an infection occurring after the index date (ever-treated). Follow-up was censored at the first occurrence of a significant infection event, end of eligibility, or end of study period. Data were analyzed using Cox regression.

Results: In 13,752 NS and 2293 S patients, time-stratified rates declined 2- to 3-fold between the first year versus ≥2 years. Risk of significant infection was not different for either attribution model [90-day hazard ratio (HR) = 0.93, 95CI: 0.74 to 1.17, $P = 0.55$; ever treated HR = 0.94, 95CI: 0.78 to 1.15, $P = 0.57$]. First and second year rates were similar. Predictors included age ≥50 years; history of significant or opportunistic infection, diabetes, respiratory disease; Charlson score ≥2; or prior hospitalizations.

Conclusions: The risk of a significant infection was not different between NS and S patients. Regardless of switching status, the rate of infection was greater in the first year. This study was limited by the lack of clinical data to determine the reason for switching.

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Patients with rheumatoid arthritis (RA) are often treated with tumor necrosis factor-α (anti-TNF) inhibitors. Anti-TNF (aTNF) agents have been shown to improve signs and symptoms, slow radiographic progression, and improve quality of life for patients with RA (1). Studies of the risk of infections among aTNF agents relative to other treatments such as disease-modifying anti-rheumatic drugs (DMARDs) have yielded mixed results, with some finding higher frequency of infections and others showing no difference (2-7). Patients experiencing therapeutic failure or adverse events while on one aTNF agent are commonly switched to another aTNF agent. Epidemiologic studies of significant infections in RA patients who switch aTNF agents have been limited by small sample sizes, short study periods, or other design features. In this study, a large claims database was used to describe and compare rates of significant infections in aTNF drug nonswitchers (NS) and switchers (S) over a 7-year period.

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MATERIALS AND METHODS

Data Source and Patients

The Thomson Reuters MarketScan database was used to obtain patient data (8). The database contains the administrative medical and pharmacy experience of privately insured individuals from more than 100 health plans in the United States with supplemental Medicare data.

The study period was from January 1, 2000 to December 31, 2007. Subjects had at least one year of continuous medical and pharmacy eligibility during the study preceding the index date. Subjects under the age of 18 years old at the index date were excluded.

RA was defined in patients with at least 2 claims for International Classification of Diseases–9th Revision–Clinical Modification (ICD-9-CM) diagnoses code 714.0 or 714.2 within the 365 days prior to the first claim for an aTNF agent in the study period.

Three aTNF agents were available during the study period: infliximab, etanercept, and adalimumab. These agents were identified by either an occurrence of a Healthcare Common Procedure Coding System code or a National Drug code on at least one claim during the study period.

Subjects that switched from one aTNF agent to a second aTNF agent during the study period were assigned to the S cohort. The index date for this group was the date of the first claim for the second aTNF agent in the study period.

Control subjects with only one aTNF agent identified throughout their study period were assigned to the NS cohort. The index date was defined as the date of the first aTNF agent claim.

Eligible subjects were required to have a 365-day lead-in period before the first aTNF drug claim. This selection criterion was used to so that the first exposure to an aTNF agent represented a new or inception treatment.

The analysis described in this report focused on the eligibility period that contained the index date. Subsequent eligibility periods were not analyzed.

Outcome Definitions

Significant infections were identified using selected ICD-9-CM codes and any of the following definitions below:

- Infections resulting in hospitalization: any disease/condition listed in the final outcome definition that was coded in any of the 15 diagnosis fields of an inpatient admission claim.
- Infections resulting in administration of intravenous antibiotics: any disease/condition listed in the final outcome definition that was coded in any of the 9 diagnosis fields of an outpatient services claim and which was treated with an intravenous antibiotic as defined by specific Healthcare Common Procedure Coding System code or a National Drug code. Intravenous antibiotic therapy could not be more than 7 days before or 7 days after the infection diagnosis.
- Clinically important infections: A specific list of serious diseases that may appear without regard to the claim service setting that included tuberculosis, leprosy, diseases caused by other mycobacteria, diphtheria, whooping cough, meningococcal infection, tetanus, poliomyelitis/other nonarthropod viral diseases of central nervous system, viral hepatitis, syphilis and other venereal diseases, or mycoses.

Data Analysis

Patient demographics for age, gender, and region were collected. In addition, administrative variables of eligibility time and postindex follow-up time were described. Baseline history variables were defined as diagnoses or medications coded in the 365-day lead-in period prior to the index date. These variables included history of significant infections, history of opportunistic infections, Charlson comorbidity Index (CCI) scores, switching patterns between aTNF agents, history of joint surgery, history of diabetes, history of asthma/chronic obstructive pulmonary disease (COPD), history of any oral corticosteroid therapy, presence of disease-modifying anti-rheumatic drugs in the 1-year period prior to index, and number of hospitalizations.

The modified CCI score was used as a proxy variable for the burden of comorbidities among the cohorts. Diseases comprising the CCI were mapped to ICD-9-CM codes (9,10). The mapped comorbidities included myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, gastrointestinal ulcer, chronic liver disease, hemiplegia, moderate or severe kidney disease, diabetes, diabetes with complication, tumor, leukemia, lymphoma, moderate or severe liver disease, malignant tumor, metastasis, acquired immune deficiency syndrome.

Two models that define the exposure period (ie, "treatment attributable at-risk period" (11)) were used to detect a significant infection.

90-day Exposure Model

A 90-day exposure period was assigned for every aTNF agent claim starting at the index date. From the dispensing date, each claim was assigned an exposure period for the shorter of (1) 90-days exposure, (2) days from the claim until end of eligibility, or (3) days from the claim until a succeeding claim for the same drug. If an aTNF claim for the same drug occurred before the end of a 90-day exposure period, then a new exposure period was started with any overlap counted only once. The first significant infection that occurred within an aTNF drug exposure period was counted and entered into incidence calculations and the regression model.

This model relies on an exposure period of 90 days within which a significant infection may be attributed to the drug. A significant infection occurring outside of the 90-day exposure period from an aTNF claim may exist but it would not have been counted as an event in this

model. The 90-day model could be considered a high-specificity model for attributing significant infection event to an aTNF agent.

"Ever-Treated" Exposure Model

The exposure period started on the index date and continued until (1) the end of eligibility or (2) the end of the study period. The first significant infection that occurred anytime after the index date was counted in this model.

This high-sensitivity model presumed that all significant infections may be attributed to the exposure regardless of elapsed time between exposure to an aTNF agent and an event. This model counted significant infections that would have been captured in the 90-day model, and also significant infections that occurred >90 days from a claim for an aTNF agent.

Cox regression was performed to analyze the difference in time to infection between NS patients and S patients. The follow-up period—which comprises the patient–time denominator—started at the index date and was censored at either the first occurrence of the following:

- A significant infection event
- The end of eligibility, or
- The end of study period

Data evaluation was performed using SAS software version 9.1 (SAS Institute, Cary, NC).

Baseline data represented characteristics of patients in the 1-year period before the index date (ie, the 1-year period prior to the date of the 1st aTNF claim for the NS cohort, and the date of the 2nd aTNF claim for the S cohort). The regression for both attribution models was adjusted, without removal, for specific baseline data: age at index (categorical variables): 18 to 39 (referent), 40 to 49, 50 to 59, 60 to 69, and ≥70 years; gender; cumulative number of hospitalizations; modified Charlson comorbidity score; history of significant infection; history of opportunistic infections; history of joint surgery; use of DMARDs excluding methotrexate at baseline; methotrexate use at baseline; oral corticosteroid use; history of diabetes; and history of COPD or asthma.

RESULTS

For the observation period of January 1, 2001 to December 31, 2007, a total of 16,045 RA patients met the selection criteria for this study (Fig. 1). Of these, 13,752 RA patients (86.7% of total) met the definition for the NS cohort, and 2293 (14.3%) met the definition for the S cohort. Women comprised about 75% of the NS cohort, and 78% of the S cohort. Age between the 2 groups was

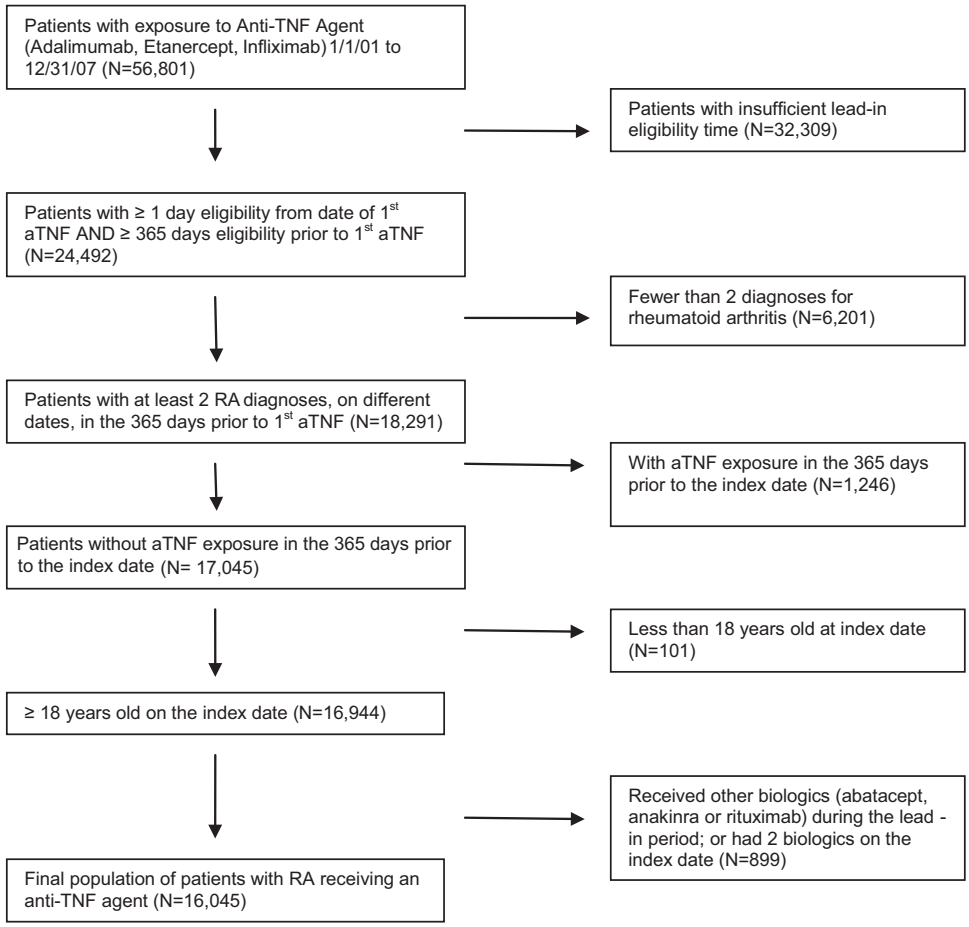

Figure 1 Selection of rheumatoid arthritis subjects taking anti-TNF agents.

Table 1 Characteristics[a] of Subjects with Rheumatoid Arthritis Receiving Anti-TNF Therapy, MarketScan Database, January 1, 2001 to December 31, 2007

Characteristics	Nonswitchers		Switchers		
	N	%	*N*	%	χ^2
All	13,752	100.0	2293	100.0	
Gender					<0.001
Male	3470	25.2	496	21.6	
Female	10,282	74.8	1797	78.4	
Age group (at index date)					0.015
18-39	1404	10.2	225	9.8	
40-49	2531	18.4	427	18.6	
50-59	4462	32.4	776	33.8	
60-69	3165	23.0	561	24.5	
≥70	2190	15.9	304	13.3	
Mean age	56.1		55.7		
Charlson comorbidity score					0.366
0	11,089	80.6	1851	80.7	
1	1484	10.8	254	11.1	
2	832	6.1	126	5.5	
3	182	1.3	32	1.4	
≥4	165	1.2	30	1.3	
Number of hospitalization					0.053
0	11,721	85.2	1892	82.5	
1	1618	11.8	309	13.5	
2	320	2.3	71	3.1	
3	67	0.5	16	0.7	
≥4	26	0.2	5	0.2	
History of significant infection	983	7.1	205	8.9	0.002
History of opportunistic infection	1397	10.2	274	11.9	0.009
History of DMARD use	6546	47.6	1086	47.4	0.832
History of methotrexate use	9994	72.7	1498	65.3	<0.001
History of oral corticosteroid use	8995	65.4	1612	70.3	<0.001
History of diabetes	1922	14.0	331	14.4	0.558
History of asthma/COPD	2957	21.5	608	26.5	<0.001
History of joint surgery	1000	7.3	186	8.1	0.155

COPD, chronic obstructive pulmonary disease; DMARD, disease-modifying anti-rheumatic drugs.
[a]Baseline history variables were defined as diagnoses or medications coded in the 365-day lead-in period prior to the index date.

similar with the mean age for the NS cohort slightly higher than the S cohort (56.1 versus 55.7 years). The highest proportion of patients was found in the 50- to 59-year range (Table 1). The total eligibility time for the S cohort was 8.4 months longer than NS cohort (5.5 versus 4.8 years). Total observation time was also longer by an average of 2.4 months for S than NS (1.8 versus 1.6 years). Geographic distribution of both cohorts was similar, with most of the patients coming from the South region. S cohort patients remained on their first aTNF drug for an average of 1.2 years before switching (SD = 1.0 years, median = 0.8 years).

Notable baseline differences between cohorts included greater numbers of methotrexate users (73% versus 65%, $P < 0.001$), and fewer significant infections (7.1% versus 8.9%, $P = 0.002$), corticosteroid users (65% versus 70%, $P < 0.001$), and asthma/COPD cases (21.5% versus 26.5%, $P < 0.001$) in the NS group versus the S group (Table 1). These variables were statistically adjusted in the final regression model.

Etanercept was most often used as the first aTNF agent in both cohorts (43% NS, 45% S, $P = 0.07$). S patients were most frequently switched to adalimumab (43%), followed by etanercept (33%). As a percentage of the combined total of RA patients starting each aTNF agent, the proportion of patients switching away from infliximab (15.4%), adalimumab (16.7%), and etanercept (17.1%) was similar.

Among the S cohort, nearly 79.5% of patients made one drug switch, whereas 16.6% switched drugs twice, and 3.9% switched drugs 3 or more times. These included all types of switches including switching back to previous aTNF agents.

Significant Infections

Significant upper and lower respiratory infections were most common in both groups. Other sites of frequently recorded significant infections were skin or soft tissue (cellulitis), bloodborne (septicemia), liver (viral hepatitis) and kidney (pyelonephritis). In the 90-day model, significant

Table 2 Incidence Rates of First Infection, by Type, During Entire Available Period in Nonswitchers and Switchers Using 2 Attribution Models, MarketScan Database, January 1, 2001 to December 31, 2007

	90-d Model: All Patients = 16,045 All PY = 26,502								Ever-Treated Model: All Patients = 16,045 All PY = 25,866							
	Nonswitchers (*n* = 13,752; PY = 23,196)				Switchers (*n* = 2293; PY = 3306)				Nonswitchers (*n* = 13,752; PY = 22,625)				Switchers (*n* = 295; PY = 3112)			
Infection Type	No. of Cases	Incidence Rate (/100 PY)	95% Confidence Interval		With Specified Infection	Incidence Rate (/100 PY)	95% Confidence Limits		No. of Cases	Incidence Rate (/100 PY)	95% Confidence Limits		With Specified Infection	Incidence Rate (/100 PY)	95% Confidence Limits	
Significant infection	1464	6.31	6.00	6.63	224	6.78	5.94	7.69	1464	6.47	6.15	6.80	224	7.20	6.31	8.16
Hospitalized infection																
Overall	909	3.92	3.67	4.18	128	3.87	3.24	4.59	909	4.02	3.77	4.28	128	4.11	3.44	4.87
Sepsis	132	0.57	0.48	0.68	18	0.54	0.32	0.87	132	0.58	0.49	0.69	18	0.58	0.34	0.92
Pneumonia	347	1.50	1.34	1.66	40	1.21	0.87	1.65	347	1.53	1.38	1.70	40	1.29	0.92	1.75
Urinary tract	44	0.19	0.14	0.26	9	0.27	0.12	0.53	44	0.19	0.14	0.26	9	0.29	0.13	0.56
Skin	154	0.66	0.56	0.78	20	0.60	0.37	0.94	154	0.68	0.58	0.80	20	0.64	0.39	1.00
Tuberculosis	20	0.09	0.05	0.13	3	0.09	0.02	0.28	20	0.09	0.05	0.14	3	0.10	0.02	0.30
Opportunistic infections	221	0.95	0.83	1.09	38	1.15	0.81	1.58	221	0.98	0.85	1.11	38	1.22	0.87	1.68
Serious infections[a]	1274	5.49	5.20	5.79	192	5.81	5.03	6.65	1274	5.63	5.33	5.93	192	6.17	5.34	7.07
Clinically important infections[b]	190	0.82	0.71	0.94	32	0.97	0.66	1.37	190	0.84	0.73	0.97	32	1.03	0.70	1.46

PY, person-years.
[a]Includes hospitalized infections or infections requiring intravenous antibiotics; excludes "Clinically Important Infections."
[b]A select list of infections which appear without regard to the claim service setting.

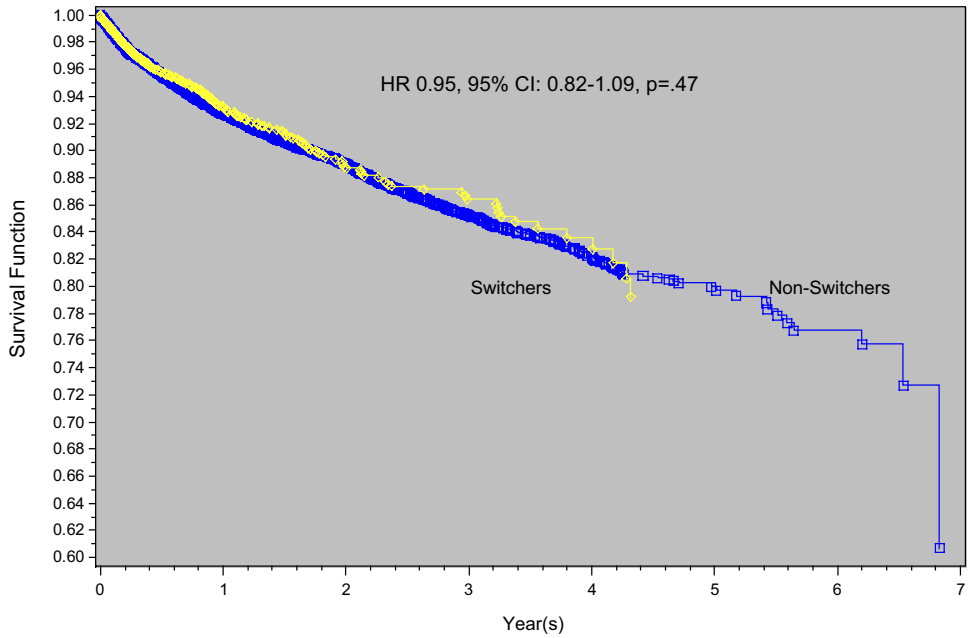

Figure 2 Survival plots for significant infection in rheumatoid arthritis patients receiving anti-TNF agents (90-day model, nonswitchers referent). Regression model adjusted for age at index (categorical variables): 18 to 39 (referent), 40 to 49, 50 to 59, 60 to 69, and ≥70 years; gender; cumulative number of hospitalizations; modified Charlson comorbidity score; history of significant infection; History of opportunistic infections; history of joint surgery; use of DMARDs excluding methotrexate at baseline; methotrexate use at baseline; oral corticosteroid use; history of diabetes; history of chronic obstructive pulmonary disease or asthma. (Color version of figure is available online.)

pneumonia and septicemia were recorded more often in NS than S. Conversely, proportions of significant kidney infections and significant bronchitis were higher in S than NS. Similar findings existed in the ever-treated model.

Significant Infections by Exposure Model

Overall, significant infections occurred in 10.5% of patients in the 90-day model and 13.7% in the ever-treated model. This trend of greater proportion of significant infections in the ever-treated model was consistent even when stratified by NS and S. NS patients had an average of 1.7 years of observation time compared to 1.4 years for S patients.

In the 90-day model, NS patients had similar rates of significant infections compared to S patients [6.31/100 person-years (PY), 95% confidence interval (CI): 6.01 to 6.62 versus 6.78/100 PY, 95% CI: 5.95 to 7.67, Table 2]. This was true across all age and gender stratifications. Men had slightly higher rates than women, and rates appeared highest in the ≥70 age group for both cohorts.

Likewise, in the ever-treated model, NS had similar rates of significant infections compared to S (8.45/100 PY, 95% CI: 8.10 to 8.80 versus 9.10/100 PY, 95% CI: 8.15 to 10.12, Table 2). This was true across age and gender stratifications. Rates in the ever-treated model were generally higher than that of the 90-day model. As in the 90-day model, men had slightly higher rates than women, and rates were highest in the ≥70 age group for both cohorts.

Adjusted hazard ratios (HR) for significant infections showed there was no difference in the risk between NS and S in either attribution model [90-day HR 0.95, 95% CI: 0.82 to 1.09, $P = 0.47$; ever-treated HR 0.96, 95% CI: 0.85 to 1.09, $P = 0.56$; Figs. 2 and 3]. Predictors of significant infection differed slightly between analysis models but included combinations of the following: age 50 to 59 (versus age 18 to 39); age 60 to 69 (versus age 18 to 39); age ≥70 (versus age 18 to 39); baseline histories of significant infections, opportunistic infections, joint surgery, diabetes, asthma/COPD, corticosteroid use; baseline Charlson comorbidity score ≥2; and increasing number of hospitalizations.

DISCUSSION

Previous studies have reported rates of serious infections in RA patients using aTNF agents; however, few studies examine differences in infection risk among RA patients initiating versus switching aTNF agents (2,5,12-18). In this study we describe rates of significant infection among privately insured RA patients treated with one versus more than one aTNF agents using data from administrative health care claims.

In this study, NS and S did not appear to be homogeneous cohorts judging from the baseline parameters measured, which underscored the importance of adjusting for medical history when comparing risk of infection in RA patients initiating or switching biologics. The S cohort had higher numbers with baseline asthma, diabetes, joint surgery, corticosteroid use, and prior significant and opportunistic infections. In addition, S patients were more

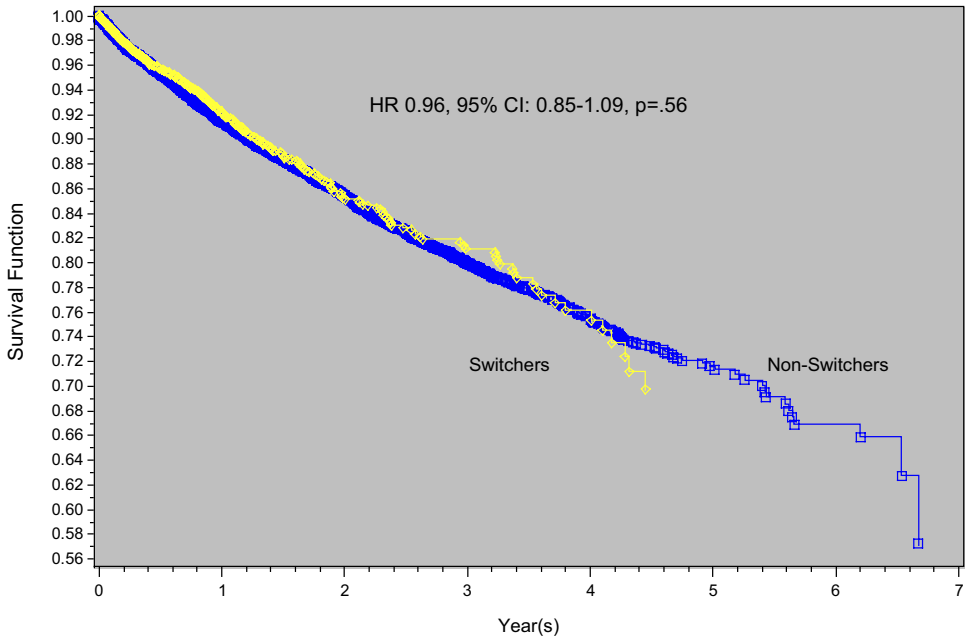

Figure 3 Survival plots for significant infection in rheumatoid arthritis patients receiving anti-TNF agents (ever-treated model, nonswitchers referent). Regression model adjusted for age at index (categorical variables): 18 to 39 (referent), 40 to 49, 50 to 59, 60 to 69, and ≥70 years; gender; cumulative number of hospitalizations; modified Charlson comorbidity score; history of significant infection; history of opportunistic infections; history of joint surgery; use of DMARDs excluding methotrexate at baseline; methotrexate use at baseline; oral corticosteroid use; history of diabetes; history of chronic obstructive pulmonary disease or asthma. (Color version of figure is available online.)

likely to be using antibiotics and had more infection diagnoses in the preindex period. Likewise, other autoimmune diseases such as lupus and Sjögren's syndrome appeared to be higher.

In general, significant infection rates in this study were similar to rates of serious infection reported in other studies (2,5,12-18). Recently Curtis and colleagues examined the risk of serious infections among RA patients switching biologic agents using 2931 treatment switch episodes over 4.5 years from another large health insurance database. They reported a mean rate of hospitalized infections of 7.0/100 PY in switchers versus 4.6/100 PY in patients treated with a first biologic agent. The authors concluded that other patient characteristics contributed to the variability in the rate of infections beyond the risk associated with switching patterns or a specific drug (6), which was consistent with the findings in our study.

As described by Dixon et al, risk windows for attributing an event to treatment can have a significant impact on risk estimation (4). To account for the possible persistence of risk after exposure to an aTNF agent, the "ever-treated" model was used to explore the rate of significant infections throughout the follow-up period. The "ever-treated" model may detect more false-positive infections, whereas the 90-day model may miss true-positive infections that lay outside of the predefined period. Performing both analyses permitted the observation of the difference between these models. Rates of significant infections were higher in the ever-treated model than in the 90-day model. This is to be expected; however, attribution of the additional infections to aTNF agents is difficult because the extended pharmacologic effects of these drugs are not well understood. Other clinical changes taking place over time were not accounted for in the study. With an increasing array of biologic agents used to treat RA, the ability to determine the period of true exposure will be more difficult.

Limitations of the data source prevent the identification of drug channeling or other patient and therapy selection factors that may play a role in influencing the rates of significant infections. aTNF inhibitors agents are typically selected after a poor response to nonbiologic DMARDs such as methotrexate. Likewise, switching to a different aTNF agent is commonly owing to primary or secondary lack of effectiveness or from adverse events.

In addition, drug switching or discontinuation may be influenced by either therapeutic failure, adverse events, or even the risk of adverse events based on clinical judgment. During the observation period (2001-07), data on the risk of infection were being uncovered in scientific reports, which may have influenced treatment patterns in ways that were not captured in this study (6,10). Again, the clinical or health service related reasons for changing drug therapy could not be measured in this study. A 1-year lead-in period without exposure to aTNF agents opens the possibility that some patients in the NS group may be misclassified if they received an aTNF agent >1 year before the index date. Although baseline corticosteroid use was

adjusted for in this analysis, residual confounding because of dose, duration, or proximity to aTNF therapy may still exist, which may influence the rate of infection between cohorts. Last, the database did not capture race or ethnicity of subjects, so differences in this variable could not be accounted for.

In this study of RA patients receiving aTNF agents, switching drugs does not appear to alter the risk of significant infection. Further exploration may include analyses by individual drugs, further study of time-to-event, and accounting for other patterns underlying the health care system that may influence the risk of significant infection.

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.semarthrit.2012.04.001.

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