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ORIGINAL ARTICLE

Use of a Disease Risk Score to Compare Serious Infections Associated With Anti–Tumor Necrosis Factor Therapy Among High- Versus Lower-Risk Rheumatoid Arthritis Patients

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Objective. **To evaluate whether rates of serious infection with anti–tumor necrosis factor (anti-TNF) therapy in rheumatoid arthritis (RA) patients differ in magnitude by specific drugs and patient characteristics.**

Methods. **Among new nonbiologic disease-modifying antirheumatic drug users enrolled in Medicare and Medicaid or a large US commercial health plan, we created and validated a person-specific infection risk score based on age, demographics, insurance type, glucocorticoid dose, and comorbidities to identify patients at high risk for hospitalized infections. We then applied this risk score to new users of infliximab, etanercept, and adalimumab and compared the observed 1-year rates of infection to one another and to the predicted infection risk score estimated in the absence of anti-TNF exposure.**

Results. **Among 11,657 RA patients initiating anti-TNF therapy, the observed 1-year rate of infection was 14.2 infections per 100 person-years in older patients (age ≥65 years) and 4.8 in younger patients (age <65 years). There was a relatively constant rate difference of ~1–4 infections per 100 person-years associated with anti-TNF therapy across the range of the infection risk score. Infliximab had a significantly greater adjusted rate of infection compared to etanercept and adalimumab in both high- and lower-risk RA patients.**

Conclusion. **The rate of serious infections for anti-TNF agents was incrementally increased by a fixed absolute difference irrespective of age, comorbidities, and other factors that contributed to infections. Older patients and those with high comorbidity burdens should be reassured that the magnitude of their incremental risk with anti-TNF agents is not greater than for lower-risk patients.**

INTRODUCTION

Despite the clear benefits of tumor necrosis factor antagonists (anti-TNF) in many patients with rheumatoid arthritis (RA), these agents sometimes have been associated with an increased rate of serious infections (1–7). The rate of serious infections in clinical trials and observational stud-

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Significance & Innovations

- A person-specific infection risk score to predict the 1-year risk of hospitalized infection was derived and validated among rheumatoid arthritis patients initiating nonbiologic disease-modifying antirheumatic drugs.
- Using this risk score, predicted versus observed rates of serious infections were compared among new anti–tumor necrosis factor (anti-TNF) users. There was a constant rate difference of ~1–4 infections per 100 person-years associated with anti-TNF therapy regardless of whether the patient was a low- or high-risk patient.
- Drug-specific risks of serious infections were compared between biologic agents and showed somewhat higher rates of infection for new infliximab users compared to new etanercept or adalimumab users.

ies of RA patients treated with biologic agents is typically 3–7 infections per 100 person-years. Some studies have reported that the rate of infections associated with anti-TNF therapy is ~1.5–2.0-fold higher compared to treatment with traditional nonbiologic disease-modifying antirheumatic drugs (DMARDs). However, the magnitude of the rate increase in infections associated with anti-TNF therapy is generally unknown for subgroups of patients who are at higher than average risk on the basis of older age, comorbidities, glucocorticoid use, and other factors.

When evaluating whether there is a greater infection rate associated with anti-TNF therapy for high-risk patients compared to patients at lower risk, it is useful to report measurements of association on both relative and absolute scales. For example, if the rate of serious infections associated with initiating anti-TNF therapy increased from 3 to 5 infections per 100 person-years, the incremental rate could be expressed as an absolute rate difference of 2 infections per 100 person-years, or a relative increase of 60% (i.e., an incidence rate ratio of 1.6). In contrast, for an RA patient at high baseline risk for infection on the basis of older age, significant comorbid conditions, and concurrent glucocorticoid use, that same absolute increase in the rate of 2 infections per 100 person-years, from 10 to 12 infections per 100 person-years, represents only a 20% relative increase, or an incidence rate ratio of 1.2. Therefore, the interpretation of the measurements of association expressed on a relative scale requires a clear understanding of the absolute rates, especially when comparing relative measures of association between studies and trying to harmonize results.

To assess how the risk of serious infection associated with anti-TNF therapy might vary between RA populations with different characteristics, our objectives were to build and validate a statistical model for a composite infection risk score among patients starting nonbiologic therapies, and apply that infection risk score to evaluate whether the rate of serious infection associated with individual anti-TNF agents varied for lower- versus high-risk patients.

PATIENTS AND METHODS

Eligible patient populations and observation period. We used 2 administrative databases consisting of RA patients enrolled in Medicare and Medicaid between 2000 and 2006 (the governmentally insured population) or commercially insured RA patients enrolled in Aetna, one of the largest health insurers in the US that provides benefits to >18 million individuals, between 2005 and 2010. We identified RA patients using International Classification of Disease, Ninth Revision (ICD-9)–coded physician diagnoses (see Supplementary Appendix A, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Patients became eligible for observation after they filled a new prescription for methotrexate (MTX) or other nonbiologic DMARDs (sulfasalazine [SSZ], leflunomide [LEF], or hydroxychloroquine [HCQ]) or an anti-TNF agent (infliximab, etanercept, or adalimumab). Patients with physician diagnoses for inflammatory bowel disease, ankylosing spondylitis, psoriasis, or psoriatic arthritis in a 12-month baseline period were excluded. The governmentally insured individuals were required to be age ≥65 years at the start of followup. Patients with Medicare Advantage were excluded since their information was not complete within this data source. The commercially insured patients were required to be age <65 years at the start of followup, and their followup time could extend past age 65 years only if they were enrolled in the health plan through Medicare Advantage with a pharmacy benefit. Any other type of coverage by the health plan for these individuals was often a secondary payor to government insurance (i.e., Medicare), and therefore the enrollees' claims history in the health plan data may be incomplete. These age restrictions were in accordance with the recommendation that the effect of comorbidities and other risk factors can be more accurately modeled within more homogeneous age strata (8). Additional details about the characteristics and infection risks in these cohorts have been previously published (7,9,10).

The infection risk score. *Nonbiologic DMARD population.* After meeting the above eligibility criteria, we derived the infection risk score in a population of RA patients newly initiating a nonbiologic DMARD. This population consisted of RA patients with at least 1 prescription for MTX, LEF, SSZ, or HCQ. Because SSZ and HCQ are sometimes used for RA patients with more mild disease, we required that SSZ and HCQ patients must also have been receiving MTX in the preceding year to identify patients with a higher degree of RA severity. The date the first time the prescription was filled for any of these 4 medications defined the index date, marked the start of a treatment episode, and began the followup time. To be considered a new user of each of these drugs, individuals could not have received the agent in the preceding 12 months (11). Patients must have had medical and phar-

macy benefits in the 12 months prior to the index date and throughout followup.

Nonbiologic DMARD populations were identified from the governmentally insured and commercially insured databases. The methods described below were applied to both the governmentally and commercially insured RA populations to assess the robustness of the study findings.

Definition of serious infection outcome. The outcome of interest was the first hospitalization for any type of infection during the first year of followup. We identified hospitalizations for infections using ICD-9–coded discharge diagnoses. The ICD-9 codes used to identify infections were initially identified through a literature review and showed good performance in 2 separate validation studies that used medical chart reviews to confirm infections (1,12). To increase the likelihood that a patient was hospitalized for infection, infection diagnosis codes were identified in the primary discharge diagnosis field of the Medicare data. An analogous procedure was followed for the commercially insured population.

Design of the infection risk score. Disease risk scores model the contribution of independent predictors to the risk of a specific outcome, allowing for multivariable reduction into a single composite measure. In this sense, risk scores are similar to propensity scores (13–15), although they model the risk for the outcome rather than the risk for exposure. The World Health Organization FRAX calculator (16) and several well-known cardiovascular risk calculators (e.g., Framingham Risk Score) (17) are examples of disease risk scores. Disease risk scores achieve similar control for confounding compared to traditional multivariable adjustment, but are more efficient when outcome data are sparse (13,14,18). We used disease risk scores rather than propensity scores because we had >2 treatment groups of interest, and optimal use of propensity scores in such a situation is not well defined.

An infection risk score model was developed to predict the patients' 1-year risk (i.e., the rate at 1 year) of a hospitalized infection and was intended to capture all infection-related confounding for measured factors in the absence of exposure to biologic agents. The factors considered for inclusion in the score were those of high clinical interest and previously identified from studies in the literature (1,19). Some factors were hypothesized not to be causally related to infection, but rather served as proxies for health-seeking behaviors or health status (20–22). We used the 12-month baseline period prior to the index date for covariate assessment, except for average glucocorticoid dose, which was ascertained in the 6 months prior to the index date.

Weights for the factors in the infection risk score were derived separately within each data set. All potential risk predictors were initially included in a multivariable Cox proportional hazards model to estimate and predict infection-free survival at 1 year. Censoring occurred when patients experienced a first hospitalized infection, initiated a biologic agent (<5% of the DMARD treatment episodes), or discontinued enrollment in the health plan. Factors were retained in the Cox model based on clinical interest and if they had at least a modest association with the outcome of a hospitalized infection ($P < 0.15$). The interaction terms between age, comorbidities, and other risk factors were included as potential predictors. Model coefficients were used to compute the person-specific predicted probability of infection-free survival at day 365 after DMARD initiation.

The estimated infection risk score was then categorized into deciles and compared to the mean of the observed 1-year rate of infection in a new validation cohort constructed from 200 bootstrap samples (of equal size to the original data set) to evaluate calibration. Discrimination of the infection risk score in the validation sample was evaluated by computing the c-index (23), similar to the area under the receiver operating curve or the C statistic in logistic regression (24). Values from 0.60–0.69 were considered fair discrimination, between 0.70–0.79 good discrimination, and ≥0.80 excellent discrimination.

Evaluating the association between anti-TNF agent use in high- versus lower-risk RA patients using the infection risk score. *Anti-TNF population.* We identified RA patients in each insured population who were initiating 1 of the 3 anti-TNF agents (adalimumab, etanercept, or infliximab). To be considered a new anti-TNF user, patients must have had a new prescription or infusion with no prior use of any biologic agent in the preceding 12 months. The patients remained assigned to these exposure groups for up to 1 year after the index date irrespective of whether they continued the anti-TNF medication or not, similar to an intent-to-treat design. The patients were censored at the time of discontinuation from the health plan, death, hospitalized infection, or with a switch to a different biologic agent. The patients could at most contribute a single treatment episode for each of the 3 anti-TNF agents.

Comparing the rate of serious infections associated with the 3 anti-TNF agents to the infection risk score and to each other. We obtained the infection-related risk factor information from the baseline data assessed in the 12 months preceding the initiation of anti-TNF therapy. Using each person's baseline risk factors and the weights from the infection risk score derived in the nonbiologic DMARD population, we computed the infection risk score for each individual initiating anti-TNF therapy. For each of the 3 anti-TNF medication groups, patients with an infection risk score that was higher than the maximum value of any patient in the other 2 anti-TNF groups were excluded, similar to the trimming of propensity score tails (25–27). This ensured that the range of the infection risk scores was similar for each of the anti-TNF groups.

For illustration purposes, patients were categorized into lower versus high infection risk groups according to deciles of the infection risk score. For each anti-TNF drug separately, we calculated the observed 1-year rate of infection for each decile of the infection risk score. These data were plotted graphically using loess curves (28) to contrast the observed infection rates by drug across the range of predicted infection risk scores.

Cox proportional hazards models were used to directly compare the 1-year rate of infection for infliximab (referent) to etanercept and adalimumab, controlling for the decile of the infection risk score. Because the patients who were treated shortly after anti-TNF therapy became avail-

able might have been sicker and therefore at higher risk for infection than those treated later, a sensitivity analysis restricted infliximab patients to those initiating treatment in 2004 or later to provide a temporally comparable comparator group for adalimumab patients. The proportional hazards assumption was verified by inspecting the martingale residuals visually over the followup time. Because the patients were allowed to contribute 1 episode to >1 anti-TNF drug as a new user, SEs were adjusted to reflect the clustered nature of the data using the Huber-White sandwich method (29). All analyses were performed using SAS, version 9.2. The study was approved by the University of Alabama at Birmingham Institutional Review Board.

RESULTS

The RA patients with government insurance had a mean age of 74 years and a high prevalence of diabetes mellitus, chronic obstructive pulmonary disease (COPD), and other comorbidities (Table 1). Approximately 50% used oral glucocorticoids. In contrast, the commercially insured RA patients were younger (mean age 49 years) and had a substantially lower prevalence of all comorbidities; ~40% used oral glucocorticoids.

In the governmentally insured RA patients, 1,549 hospitalized infections occurred in the year after the start of followup among 14,693 patients in the new nonbiologic DMARD cohort contributing 11,676 patient-years, yielding an overall rate of 13.3 infections per 100 person-years. The median hospitalization duration was 6 days (interquartile range [IQR] 4–10 days). Correspondingly, 8,823 commercially insured RA patients in the new nonbiologic DMARD cohort contributed 6,453 person-years and experienced 212 hospitalized infections, yielding an overall rate of 3.3 infections per 100 person-years. The median hospitalization duration was 4 days (IQR 3–7 days). The 4 most common types of infection were similar within each population and included pneumonia, cellulitis, sepsis, and pyelonephritis.

Derivation of the infection risk score. The factors included in the infection risk prediction models in the 2 populations are shown in Table 2. Older age and various comorbidities (e.g., COPD, diabetes mellitus) were significantly associated with infection. The magnitude of the relative risk associated with each comorbidity was generally larger in the commercially insured RA patients compared to the governmentally insured RA patients. Glucocorticoids at a dosage of >7.5 mg/day were significantly associated with infections in both data sets.

Figures 1A and B show the calibration of the infection risk score for the DMARD users in both populations using the predicted infection risk from the original sample and the observed risk from the bootstrap validation sample. Calibration was generally good across the deciles of predicted infection risk. In the highest decile, the governmentally insured RA patients had an observed risk of hospitalized infection of ~45%, and an observed risk of hospitalized infection in the commercially insured RA patients was much lower at ~12%. The c-index was 0.71 (95% confidence interval [95% CI] 0.69–0.72) for the governmentally insured RA patients and 0.78 (95% CI 0.75–0.80) for the commercially insured RA patients, indicating good discrimination.

Use of the infection risk score. For both the governmentally and commercially insured patients initiating anti-TNF therapy, use of each of the 3 biologic agents was evenly distributed across the entire range of the patients' infection risk score (data not shown); moreover, few patients (<1%) had to be excluded because their infection risk score was higher than the maximum predicted risk found for patients using the other anti-TNF agents. In the governmentally insured patients, 852 hospitalized infections occurred in the year after the start of followup among 6,560 patients in the anti-TNF cohort contributing 5,997 person-years, yielding an overall rate of 14.2 infections per 100 person-years. The median length of hospitalization was 6 days (IQR 4–10 days) for the etanercept and adalimumab users and 7 days (IQR 4–11 days) for the infliximab users. Correspondingly, 5,097 commercially insured RA patients contributed 4,243 person-years and experienced 204 hospitalized infections, yielding an overall rate of 4.8 hospitalized infections per 100 person-years. The median length of hospitalization was 4 days (IQR 2–6 days) for adalimumab users, 4 days (IQR 3–6 days) for etanercept users, and 5 days (IQR 3–10 days) for infliximab users. Although the main analysis used first exposure carried forward for the 1-year followup period, if exposure was categorized using an as-treated approach with a 90-day extension, ~85% of the followup time would have been considered current exposure.

The observed 1-year rates of infection for the anti-TNF agent users were evaluated in deciles of the predicted infection risk score. For patients at the highest risk of infection (top 10%), the observed infection rates for each of the anti-TNF groups were substantially lower than predicted. For the remaining 9 deciles plotted in Figures 2A and B, the lines showing the infection rates for each of the 3 anti-TNF agents were approximately parallel to the predicted infection risk score. The magnitude of the difference between the predicted and observed rates of infection showed that there was a relatively constant, fixed increased rate of infection (~1–4 infections per 100 person-years) for the anti-TNF agent users that was greatest for infliximab users and was maintained across the deciles of the risk score. The incremental rates of infection for the adalimumab and etanercept users were lower than for the infliximab users, but still somewhat numerically higher than predicted by the infection risk score.

When directly comparing the 3 biologic agents to one another using Cox proportional hazards models, potential confounders were controlled for using deciles of predicted infection risk. The fully adjusted hazard ratio for infection comparing infliximab to etanercept was 1.52 (95% CI 1.08–2.12) and comparing infliximab to adalimumab was 1.49 (95% CI 1.05–2.10) in the commercially insured RA patients. The proportional hazards assumption was not

Table 1. Characteristics of governmentally and commercially insured biologic agent–free rheumatoid arthritis patients initiating nonbiologic DMARDs or anti-TNF therapy*

	Government insurance		Commercial insurance	
	DMARDs (n = 14,693)†	Anti-TNF (n = 6,560)‡	DMARDs (n = 8,823)§	Anti-TNF (n = 5,097)¶
Age, mean ± SD years	74.0 ± 6.3	72.8 ± 5.8	49.3 ± 10.0	47.9 ± 10.4
Women	87.6	89.7	77.3	76.5
Comorbidities				
Diabetes mellitus without complications	24.2	23.6	8.7	8.8
Diabetes mellitus with complications	5.0	5.3	1.6	1.7
COPD	27.7	27.3	12.7	12.7
Heart failure	16.2	13.4	1.2	1.0
Malignancy	6.6	5.3	3.3	2.2
Angina diagnosis	3.4	3.1	0.6	0.6
Peptic ulcer disease	3.8	4.0	0.7	0.8
Hepatitis C	0.2	0.5	0.3	0.7
Renal disease	3.8	3.4	1.4	1.4
Any fracture	7.9	8.5	3.1	3.4
Hospitalized infections				
None	79.1	80.3	93.7	93.7
1–2 episodes	12.4	11.5	4.1	4.0
≥3 episodes	8.5	8.2	2.2	2.3
Ulcer	1.8	1.7	0.2	0.1
Medications				
Prednisone, mg/day				
None	53.6	46.6	61.5	55.7
≤7.5	27.4	9.5	22.1	5.9
>7.5	19.0	43.9	16.4	38.4
Bisphosphonates	31.0	42.7	8.0	10.0
Narcotics	74.5	77.3	57.0	58.6
Antifungal medications	5.1	5.8	5.4	6.0
Hypertension medications	62.7	60.9	24.2	23.3
Antidepressants	36.6	38.8	26.4	29.6
Antihyperlipidemia medications and/or physician diagnoses	61.1	61.2	54.3	49.2
NSAIDs	65.4	64.2	51.0	49.9
Thiazide diuretics	26.5	25.9	15.0	14.8
Any intraarticular injection	0.7	0.8	0.2	0.1
Health behaviors and health services utilization				
PSA screen (men only)	49.5	51.2	28.1	23.5
Papanicolaou smear (women only)	12.7	13.5	36.2	34
Mammography (women only)	26.9	29.5	34.6	32.3
All-cause hospitalization				
0–1 hospitalization	56.9	58.2	84.2	84.9
2 hospitalizations	6.7	6.5	5.2	4.8
≥3 hospitalizations	36.4	35.3	10.6	10.3
Long-term care	3.2	2.2	NA	NA
Receiving Medicare for reasons other than age (e.g., disabled)	29.5	33.9	NA	NA

* Values are the percentage unless otherwise indicated. Governmentally insured patients were Medicare dual eligible and restricted to age ≥65 years at the start of followup. Commercially insured patients were restricted to age <65 years at the start of followup. Biologic agent–free patients had no biologic agent use in the year prior to initiation. DMARDs = disease-modifying antirheumatic drugs; anti-TNF = anti–tumor necrosis factor; COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal antiinflammatory drugs; PSA = prostate-specific antigen; NA = not applicable.
† 14,693 treatment episodes (a treatment episode is defined as new use of a medication with no prior use of that agent in the preceding year).
‡ 7,543 treatment episodes.
§ 8,823 treatment episodes.
¶ 5,635 treatment episodes.

satisfied in the governmentally insured patients; therefore, we subdivided the hazard period into ≤90 days and 91–365 days since the index date. The hazard ratio comparing infliximab to etanercept within 90 days of drug initiation was 1.56 (95% CI 1.17–2.10) and was 1.10 (95% CI 0.91–1.35) beyond 90 days. The corresponding hazard ratio comparing infliximab to adalimumab was 1.87 (95% CI 1.37–2.58) within 90 days and was 0.91 (95% CI 0.75–1.10) beyond 90 days. The sensitivity analysis that restricted infliximab patients to those initiating treatment in 2004 and beyond yielded similar results to the main analyses (data not shown).

Table 2. Risk factors for infection included in the infection risk score for governmentally and commercially insured rheumatoid arthritis patients initiating nonbiologic DMARDs*

Infection-related risk factors	Governmentally insured (n = 14,693)	Commercially insured (n = 8,823)
Age, years		
<50		Ref.
50–59		1.46 (1.00–2.15)
60–64		2.04 (1.17–3.56)
65–69	Ref.	
70–74	1.29 (1.10–1.50)	
75–79	1.61 (1.36–1.91)	
80–84	1.80 (1.47–2.21)	
≥85	2.11 (1.62–2.75)	
Women (ref. to men)	0.75 (0.59–0.95)	
Comorbidities		
Diabetes mellitus without complications	1.14 (0.99–1.32)	2.24 (1.39–3.59)
Diabetes mellitus with complications	1.74 (1.35–2.25)	4.21 (1.54–11.54)
COPD	1.41 (1.24–1.61)	1.86 (1.18–2.94)
Heart failure	1.40 (1.32–1.80)	
Malignancy	1.34 (1.06–1.68)	
Angina	0.74 (0.52–1.03)	
Peptic ulcer disease		3.81 (0.53–27.67)
Hepatitis C	2.86 (1.18–6.94)	
Renal disease	1.31 (0.98–1.74)	
Any fracture	1.22 (0.98–1.51)	
Hospitalized infections		
1–2	1.43 (1.20–1.69)	
≥3	2.74 (2.11–3.55)	
Skin ulcer (e.g., decubitus)	1.50 (0.96–2.35)	
Medications		
Prednisone, mg/day		
>0 to ≤7.5	1.03 (0.89–1.18)	1.21 (0.76–1.92)
>7.5	1.38 (1.19–1.62)	2.47 (1.63–3.72)
Narcotics	1.24 (1.07–1.44)	1.46 (1.00–2.11)
Antifungal medications	1.46 (1.13–1.88)	
Hypertension medications	1.15 (1.01–1.31)	
Antidepressants	1.22 (1.08–1.38)	1.79 (1.23–2.60)
Lipid test for screening	0.84 (0.74–0.95)	
NSAIDs	0.86 (0.76–0.98)	
Thiazide diuretics	0.86 (0.75–0.99)	0.67 (0.41–1.09)
Intraarticular glucocorticoid injection	1.53 (0.90–2.60)	
Bisphosphonates	0.87 (0.77–1.00)	2.19 (1.29–3.72)
Health behaviors and health services utilization		
PSA screen (men only)	0.73 (0.52–1.02)	
Papanicolaou smear (women only)		0.58 (0.38–0.88)
Mammography (women only)	0.88 (0.76–1.02)	
Any-cause hospitalization		
2 hospitalizations	1.18 (0.94–1.49)	1.95 (0.98–3.88)
≥3 hospitalizations	1.36 (1.17–1.58)	2.34 (1.36–4.01)
Long-term care	1.34 (1.00–1.79)	
Disabled (as the reason for entry into Medicare)	1.19 (1.04–1.36)	

* Values are the hazard ratio (95% confidence interval). The hazard ratios derived from Cox proportional hazards models correspond to the weights in the infection risk score. Factors were included in these models based on clinical interest and at least modest ($P < 0.15$) statistical association with hospitalized infection. Nonbiologic disease-modifying antirheumatic drug (DMARD) initiation is defined as new use of methotrexate, leflunomide, or sulfasalazine/hydroxychloroquine with prior use of methotrexate in the previous year. COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal antiinflammatory drugs; PSA = prostate-specific antigen.

DISCUSSION

Using 2 independent RA populations, we derived and validated an infection risk score to predict the 1-year risk of hospitalized infection for RA patients. The score demonstrated good calibration and discrimination in 2 different RA cohorts, a governmentally insured population of older individuals and a younger RA population that was commercially insured. We then demonstrated that patients treated with anti-TNF agents had a relatively constant rate of serious infection that was ~1–4 infections per 100

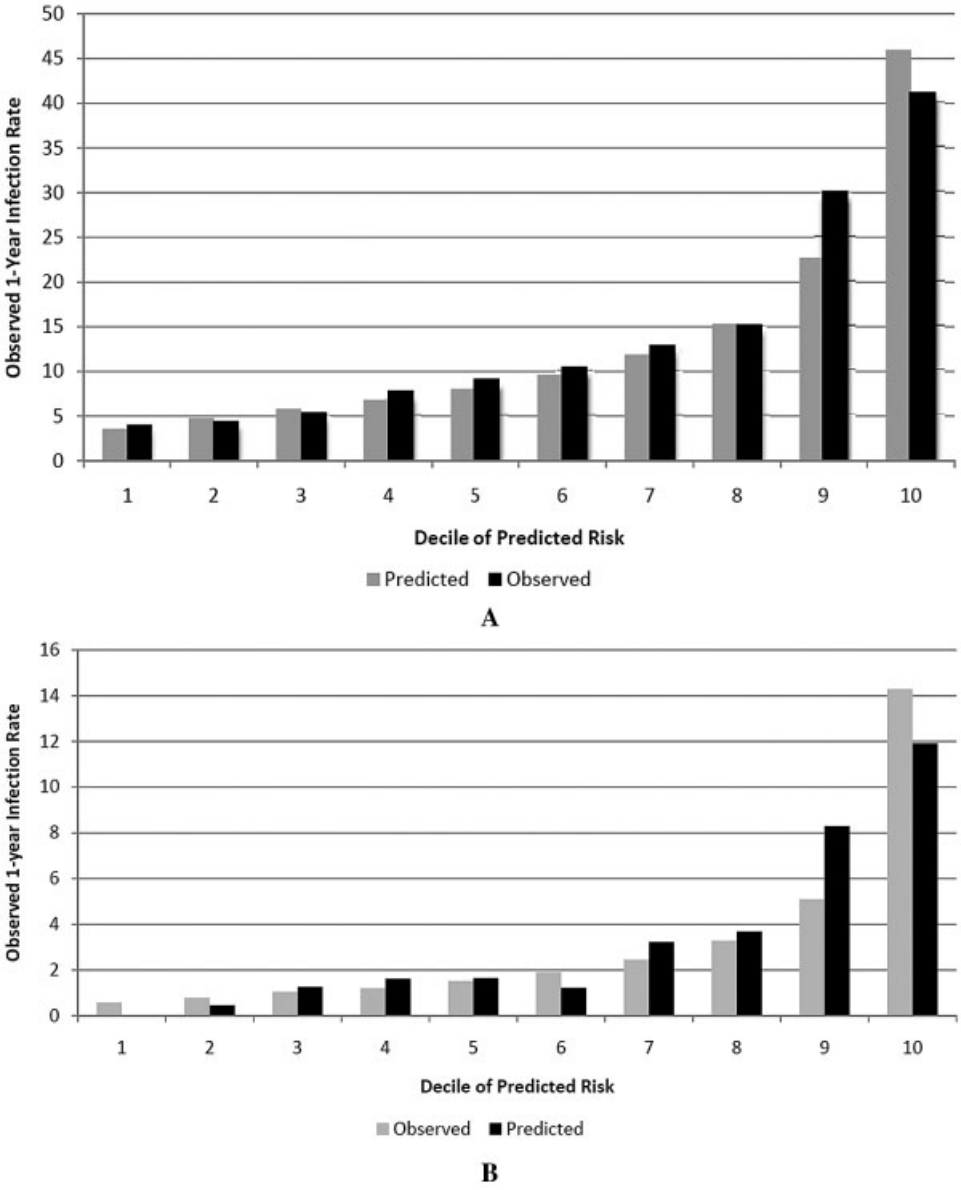

Figure 1. The predicted rate versus the observed rate (mean 1-year rate from the validation cohort derived from 200 bootstrap samples) of hospitalized infections in rheumatoid arthritis (RA) patients initiating disease-modifying antirheumatic drugs (new use of methotrexate, leflunomide, or sulfasalazine/hydroxychloroquine with prior use of methotrexate in the previous year) according to the decile of the infection risk score for governmentally insured RA patients (**A**) and commercially insured RA patients (**B**). The c-index of the model for governmentally insured and commercially insured RA patients was 0.71 (95% confidence interval [95% CI] 0.69–0.72) and 0.78 (95% CI 0.75–0.80), respectively.

person-years higher than the rate predicted by age, comorbidities, or other factors that contributed to infections independent of exposure to biologic agents. The magnitude of the difference between the observed rate and the rate predicted by the infection risk score was greatest for the infliximab users. The clinical importance of this result is that it provides reassurance for patients with a high burden of comorbidities or other strong risk factors for infection to conclude that they do not appear to have an incrementally increased rate of infection associated with anti-TNF therapy compared to lower-risk patients.

Some studies have shown an increased rate of infection associated with anti-TNF therapy (1–7). The studies that have shown an increased risk generally demonstrate average rate differences of ~2–3 infections per 100 person-years, or relative increases of 50–100% compared to use of nonbiologic DMARDs. Our results are consistent with these findings and extend these observations by providing information regarding the incremental rate of infection for patients at very low and very high risk for infection at the time of starting anti-TNF therapy. Our results are also consistent with a prior report suggesting that infection risks associated with anti-TNF therapy are similar irrespective of patient age (although age was related to infec-

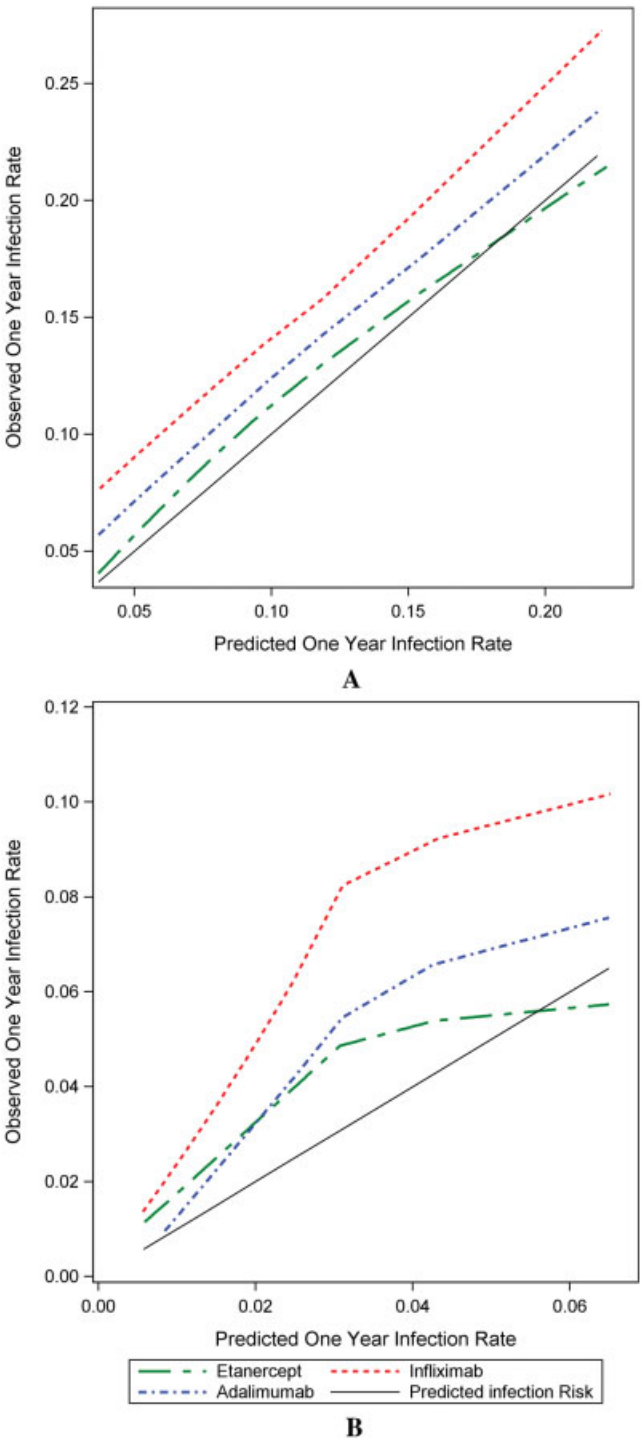

Figure 2. The observed 1-year infection rate among biologic agent–free (no biologic agent use in the year prior to initiation) rheumatoid arthritis (RA) patients treated with infliximab, etanercept, and adalimumab and enrolled in Medicare (**A**) or commercial insurance (**B**), by predicted 1-year infection rate. All patients must have had an infection risk score within the minimum and maximum range of each anti–tumor necrosis factor group; otherwise, they were excluded.

tion risk) (30). Additionally, we found modest differences between predicted and observed infection rates that were higher for some anti-TNF agents (e.g., infliximab) compared to others. This finding has been previously reported using an outcome of all serious infections (7,31) and opportunistic infections (32,33). However, modest differences in rates between anti-TNF agents, or between the observed rate in any anti-TNF agent group and the rate predicted in the absence of anti-TNF exposure, were generally overshadowed by the much larger and more heterogeneous rates of infection associated with age, comorbidities, and glucocorticoid use. In fact, based on our results, if younger patients using prednisone >7.5 mg/day were able to discontinue glucocorticoids after initiating anti-TNF therapy, the net effect would be an overall decrease in the rate of serious infections. Based on information from a survey of 446 members of the American College of Rheumatology who were rheumatologists, rate differences <5% (as we found for each of the 3 anti-TNF agents) may not have a large impact in the decision to avoid anti-TNF therapy (34).

A particular strength of this study was that the governmentally insured population that we examined had a baseline rate of infection (14 infections per 100 person-years) that was higher than that typically observed in many RA cohorts (35). Although older age and a higher prevalence of comorbidities may account for this observation, a healthy worker effect may have played a role (36). Inclusion of this high-risk population allowed us to predict and observe infection risk across a wide spectrum of infection-related risk factors, including older age, various comorbidities, and patient factors, that differed appreciably from the younger and lower-risk commercially insured population. Consistent with most RA cohort studies that observed rates of serious infections between 3 and 6 infections per 100 person-years, we demonstrated a relatively constant fixed rate difference associated with anti-TNF therapy (~1–4 infections per 100 person-years) in both RA populations. The magnitude of the rate ratios for anti-TNF use was lower (1.1–1.2) in the older RA patients compared to the corresponding rate ratios (1.5–1.6) in the younger, lower-risk RA patients. This apparent discordance in results between our 2 RA populations when expressed on the rate ratio scale was resolved by instead expressing the results on the rate difference scale. Rate differences are less dependent on the population's underlying rate of infection and may allow for better comparability between studies conducted in heterogeneous RA populations. Because rate differences are usually unadjusted, cohorts matched on a disease risk score or a propensity score (or both) may be most easily compared in this fashion. Future safety analyses would facilitate comparison between studies by reporting both crude and adjusted risk (or rate) differences, as well as ratios.

The additional strengths of our study included the derivation and application of an infection risk score at the time of initiation of a new DMARD or anti-TNF therapy, which is the most clinically relevant time at which infection risk is likely to be considered. Additionally, we derived and validated the infection risk score in the nonbiologic DMARD population rather than among the anti-TNF agent users to avoid including any incremental risk of infection associated with biologic agents in the infection

score. The methods that might allow for derivation of the risk score among anti-TNF–treated patients require assumptions such as no interaction between anti-TNF exposure and other infection risk factors. Indeed, a previous study has shown that anti-TNF therapy may decrease infection risk over time, in part mediated through reduced glucocorticoid use and improved functional status (37), making this assumption tenuous. We avoided this assumption by deriving the score in the DMARD users unexposed to anti-TNF agents and showing that the predicted infection risk score applied to anti-TNF–exposed patients had good calibration, except perhaps at the highest end of the risk spectrum where the observed risks were lower than the predicted risks for all 3 anti-TNF agents. This pattern suggests that patients at the highest risk for infection may have been channeled away from anti-TNF therapy. Finally, our procedures to identify the serious infection outcome have been validated (1,12) and were shown to have high positive predictive value compared to a gold standard of medical record review.

Because our analysis was based on administrative data, we were not able to include clinical factors, such as RA disease activity or severity, functional status, or markers of inflammation (e.g., C-reactive protein). Administrative data may misclassify some risk factors, including smoking or obesity. We assigned patients to the anti-TNF groups using an intent-to-treat approach. While this approach avoids bias for patients that discontinue or switch therapies if they experience symptoms suggestive of impending infection (38), it may misclassify exposure if there is substantial switching or discontinuation prior to 1 year. Reassuringly, we observed that 80–85% of person-time attributed to anti-TNF use would have been considered exposed using an as-treated analysis. Finally, our results focused on 2 specific populations, older patients eligible for Medicare and Medicaid (who typically qualify for insurance on the basis of age, disability, and/or lower income) and younger, commercially insured patients. Our results and the weights for the infection risk factors may not be generalizable to other cohorts (e.g., patients without insurance). As suggested by the results in Table 2 showing that infection risk factors differed somewhat between the cohorts, the weights for the infection risk factors should be rederived within the specific target population in which they will be applied, if possible.

In conclusion, among RA patients without recent exposure to biologic agents, we found that the rates of serious infection associated with anti-TNF therapy varied modestly between the agents and were increased by approximately the same fixed rate difference (~1–4 infections per 100 person-years) regardless of the patients' comorbidities, age, and other independent risk factors for infection. Patients and clinicians should be reassured that higher-risk patients do not have a further increased rate of infection with anti-TNF therapy compared to lower-risk patients. The infection risk score developed in the current analysis can likely be used in future studies to control for confounding and to contextualize safety results for therapies with biologic agents.

AUTHOR CONTRIBUTIONS

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

Study conception and design. Curtis, Xie, Chen, Muntner, Grijalva, Mcmahan, Baddley, Saag, Delzell.

Acquisition of data. Curtis, Xie, Spettell, Fernandes, Saag, Delzell.

Analysis and interpretation of data. Curtis, Xie, Chen, Muntner, Grijalva, Baddley, Saag, Beukelman, Delzell.

ADDITIONAL DISCLOSURES

Authors Spettell and Fernandes are employees of Aetna. Author Mcmahan is an employee of Aetna Pharmacy.

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