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Use of a Disease Risk Score to Compare Serious Infections Associated with Anti-TNF Therapy among High versus Lower Risk Rheumatoid Arthritis Patients

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Abstract

Background/Purpose—To evaluate whether rates of serious infection with anti-TNF therapy in rheumatoid arthritis (RA) patients differ in magnitude by specific drugs and patient characteristics.

Methods—Among new non-biologic disease modifying anti-rheumatic drug (DMARD) users enrolled in Medicare/Medicaid or a large U.S. commercial health plan, we created and validated a person-specific infection risk score based upon age, demographics, insurance, 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 one-year rate of infection to each other and to the predicted infection risk score estimated in the absence of anti-TNF exposure.

Result—Among 11,657 RA patients initiating anti-TNF therapy, the observed one year rate of infection was 14.2 per 100 person-years in older patients (>= 65 years) and 4.8 in younger patients (< 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.

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JRC: (Research grants & consulting): UCB, Roche/Genentech, CORRONA, Centocor, Amgen, BMS, Abbott
ED: (Research grants): Amgen
JB: (Consulting): Abbott, Merck
KS: Consulting (Lilly, Merck, Novartis, Savient, Ardea, URL, Regeneron, Abbott, Amgen)
CS: Stockownership: own a minimal number of shares of Aetna stock
JF: employed by Aetna
R.M: employment Aetna Pharmacy
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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 incremental risk with anti-TNF agents is not greater for them than for lower risk patients.

Keywords

rheumatoid arthritis; infection; anti-TNF; DMARD; prediction

Introduction

Despite clear benefits of tumor necrosis factor antagonists (anti-TNF) for 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 infection among biologic-treated RA patients in clinical trials and observational studies is typically 3 to 7 per 100 person-years. Some studies have reported that the rate of infection associated with anti-TNF therapy is approximately 1.5 to 2.0 fold higher compared to treatment with traditional non-biologic disease modifying anti-rheumatic 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 lower risk patients, 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 per 100 person-years, the incremental rate could be expressed as an absolute rate difference of 2 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 co-morbid conditions, and concurrent glucocorticoid use, that same absolute increase in the rate of 2 per 100 person-years, from 10 to 12 per 100 person-years, represents only a 20% relative increase, or a rate ratio of 1.2. Thus, 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: 1) build and validate a statistical model for a composite infection risk score among patients starting non-biologic therapies; and 2) apply that infection risk score to evaluate whether the rate of serious infection associated with individual anti-TNF agents varied for lower vs. high risk patients

Methods

Eligible patient populations and observation period

We used two administrative databases consisting of: 1) RA patients enrolled during 2000–2006 in Medicare + Medicaid (the ‘governmentally insured’ population), or 2) commercially insured RA patients enrolled during 2005–2010 in Aetna, one of the largest health insurers in the United States that provides benefits to more than 18 million individuals. We identified RA patients using International Classification of Disease, 9th edition (ICD-9) coded physician diagnoses. Patients became eligible for observation after they filled a new

prescription for methotrexate or other non-biologic DMARD (sulfasalazine [SSZ], leflunomide [LEF], hydroxychloroquine [HCQ]) or an anti-TNF agent (infliximab, etanercept, adalimumab). Patients with physician diagnoses for inflammatory bowel disease, ankylosing spondylitis, psoriasis, or psoriatic arthritis in a twelve month baseline period were excluded. Governmentally insured individuals must have been age 65 or older at the start of follow-up. Patients with Medicare Advantage were excluded since their information is not complete within this data source. Commercially insured patients were required to be age less than 65 at the start of follow-up, and their follow-up time could extend past age 65 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 is often a secondary payor to governmental insurance (i.e. Medicare), and therefore enrollees' claims history in the health plan data may be incomplete. These age restrictions were in accordance with recommendations that the effect of comorbidities and other risk factors can be more accurately modeled within more homogeneous age strata (8). Additional details about characteristics and infection risks in these cohorts have been previously published (7, 9, 10).

Derivation of the Infection Risk Score

Non-biologic DMARD Population—After meeting the above eligibility criteria, we derived the infection risk score in a population of RA patients newly initiating a non-biologic DMARD. This population consisted of RA patients with at least one 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 on MTX in the preceding year so as to identify patients with a higher degree of RA severity. The date of the first prescription fill for any of these four medications defined the 'index date', marked the start of a 'treatment episode', and began follow-up 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 pharmacy benefits in the 12 months prior to the index date and throughout follow-up. Non-biologic 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 follow-up. We identified hospitalizations for infections using ICD9 coded discharge diagnoses. The ICD9 codes used to identify infections were initially identified through literature review and showed good performance in two 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 in the Medicare data. An analogous procedure was followed for the commercially-insured population.

Derivation 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) except that 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) (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 more than 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 patients' one year risk (i.e. rate at one year) of a hospitalized infection and was intended to capture all infection-related confounding for measured factors in the absence of exposure to biologics. Factors considered for inclusion in the score were those of high clinical interest and previously identified 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 dataset. All potential risk predictors initially were included in a multivariable Cox proportional hazards model to estimate and predict infection-free survival at one year. Censoring occurred when patients experienced a first hospitalized infection, initiated a biologic (< 5% of DMARD treatment episodes), or discontinued enrollment in the health plan. Factors were retained in the Cox model based upon clinical interest and if they had at least modest association with the outcome of hospitalized infection ($p<0.15$). 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 start.

The estimated infection risk score was then categorized into deciles 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 dataset) 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 a receiver-operator curve or a c-statistic in logistic regression (24). Values from 0.60–0.69 are considered fair discrimination, between 0.70–0.79 good discrimination, and >=0.80 excellent discrimination.

Use of the Infection Risk Score to Evaluate the Association between Anti-TNF Use in Higher versus Lower Risk RA Patients

Anti-TNF Population—We identified RA patients in each insured population who were initiating one of three anti-TNF agents (adalimumab, etanercept, 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. 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. They were censored at the time of discontinuation from the health plan, death, hospitalized infection, or with switch to a different biologic agent. Patients could contribute at most a single treatment episode for each of the three anti-TNF agents.

Comparing the Rate of Serious Infections Associated with the Three Anti-TNF Agents to the Infection Risk Score and To Each Other—We obtained infection-related risk factor information from baseline data assessed in the 12 months preceding initiation of anti-TNF therapy. Using each person's baseline risk factors and the weights from the infection risk score derived in the non-biologic 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

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 one-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 one year rate of infection for infliximab (referent) to etanercept and adalimumab, controlling for the decile of the infection risk score. Because patients treated shortly after anti-TNF therapy became available might have been sicker and therefore at higher risk for infection than those treated later, a sensitivity analysis restricted infliximab patients to those initiating in 2004 or later so as to provide a temporally-comparable comparator group for adalimumab patients. The proportional hazards assumption was verified by inspecting the martingale residuals visually over the follow-up time. Because patients were allowed to contribute one episode to more than one anti-TNF drug as a new user, standard errors were adjusted given for the clustered nature of the data using the Huber-White Sandwich method (29). All analyses were performed using SAS 9.2 (SAS Institute, Cary NC). The study was approved by the university institutional review board.

Results

RA patients with governmental insurance had mean age of 74 years and a high prevalence of diabetes, COPD, and other comorbidities (Table 1). Approximately 50% used oral glucocorticoids. In contrast, commercially insured RA patients were younger (mean age 49 years), had a substantially lower prevalence of all comorbidities; approximately 40% used oral glucocorticoids.

In governmentally insured RA patients, 1549 hospitalized infections occurred in the one year after the start of follow-up among 14,693 patients in the new non-biologic DMARD cohort contributing 11,676 patient-years, yielding an overall infection rate of 13.3 per 100 person-years. The median (IQR) hospitalization duration was 6(4,10) days. Correspondingly, 8823 commercially insured RA patients contributed 6453 person-years and experienced 212 hospitalized infections, yielding an overall infection rate of 3.3 per 100 person-years. The median(IQR) hospitalization duration was 4(3,7) days. The four 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 two populations are presented in table 2. Older age and various comorbidities (e.g. COPD, diabetes) 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 doses > 7.5mg/day were significantly associated with infections in both datasets.

Figures 1a and 1b present 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 risks from the bootstrap validation sample. Calibration was generally good across the decile of predicted infection risk. In the highest decile, governmentally insured RA patients had a predicted risk of hospitalized infection of approximately 40%, and the

predicted risk of hospitalized infection in the commercially insured RA patients was much lower, approximately 15%. The c index was 0.71 (95% CI 0.69,0.72) for governmentally insured RA patients and 0.78 (0.75,0.80) for commercially insured RA patients, indicating good discrimination.

Use of the Infection Risk Score

For both 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 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 one year after the start of follow-up among 6560 patients in the anti-TNF cohort contributing 5997 person-years, yielding an overall rate of infection of 14.2 per 100 person-years. The median (IQR) length of hospitalization was 6 (4, 10) days for etanercept and adalimumab users and 7 (4,11) days for infliximab users. Correspondingly, 5097 commercially insured RA patients contributed 4243 person-years and experienced 204 hospitalized infections, yielding an overall rate of hospitalized infection of 4.8 per 100 person-years. The median (IQR) length of hospitalization 4 (2,6) for adalimumab users, 4 (3,6) for etanercept users, and 5 (3,10) for inflixiumab users. Although the main analysis used first exposure carried forward for the one-year follow-up period, if exposure was categorized using an as-treated approach with a 90 day extension, approximately 85% of the follow-up time would have been considered current exposure.

The observed one year rates of infection for anti-TNF users was evaluated in deciles of the predicted infection risk score. For patients at 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 2b, 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 (approximately 1–4 per 100 person-years) for anti-TNF users that was greatest for infliximab users and was maintained across deciles of the risk score. The incremental rates of infection for adalimumab and etanercept users were lower than for infliximab but still numerically somewhat higher than predicted by the infection risk score.

In directly comparing the three 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 satisfied in the governmentally insured patients. Therefore, we subdivided the hazard period into <= 90 days and 91 – 365 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 2004 and beyond yielded similar results to the main analyses (not shown).

Discussion

Using two independent RA populations, we derived and validated an infection risk score to predict RA patients' one year risk of hospitalized infection. This score demonstrated good calibration and discrimination in two different RA cohorts, one a governmentally insured

population of older individuals and the other in a younger RA population that was commercially insured. We then demonstrated that anti-TNF treated patients had a relatively constant rate of serious infection that was approximately 1–4 per 100 person-years higher than the rate predicted by age, comorbidities, or other factors that contributed to infections independent of biologic exposure. The magnitude of the difference between the observed rate and that predicted by the infection risk score was greatest for infliximab users. The clinical importance of this result is to provide 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). Those that have shown increased risk generally demonstrate average rate differences of approximately 2 to 3 per 100 person-years, or relative increases of 50–100% compared to use of non-biologic DMARDs. Our results are consistent with those findings and extend those 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 also are consistent with a prior report suggesting that infection risks associated with anti-TNF therapy are similar irrespective of patients' age (30) (although age was related to infection risk). 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 both for 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, was generally overshadowed by the much larger and more heterogeneous rates of infection associated with age, comorbidities, and glucocorticoid use. In fact, based upon our results, if younger patients using more than 7.5 mg per day of prednisone 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 upon information from a survey of 446 rheumatologist members of the American College of Rheumatology, rate differences less than 5% (as we found for each of the three anti-TNF agents) may not have a large impact in the decision to avoid anti-TNF therapy(34).

As a particular strength of the study, the governmentally insured population that we examined had a baseline rate of infection (14 per 100 person-years) that was higher than 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 observe rates of serious infections between 3–6 per 100 person-years, we demonstrated a relatively constant fixed rate difference associated with anti-TNF therapy (1–4 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 two RA populations when expressed on the rate ratio scale was resolved by instead expressing 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.

Additional strengths of our study included derivation and application of an infection risk score at the time of initiation of 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 non-biologic DMARD population rather than among the anti-TNF users to avoid including in the infection score any incremental risk of infection associated with biologics. Methods that might allow for estimation 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, previous research has showed 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 these assumptions 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 observed risks were lower than predicted for all three anti-TNF agents. This pattern suggests that patients at 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 shown to have high positive predictive value compared to a gold standard of medical record review.

Because our analysis was based upon 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 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 one 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 two 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 generalizabile to other cohorts (e.g. patients with no insurance). As suggested by the results in Table 2 showing that infection risk factors differed somewhat between the cohorts, weights for the infection risk factors should be re-derived within the specific target population in which they will be applied, if possible.

In conclusion, among RA patients without recent biologic exposure, we found that rates of serious infection associated with anti-TNF therapy varied modestly between agents and were increased by approximately the same fixed rate difference (1–4 per 100 person-years) regardless of 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 use of 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 biologic therapies.

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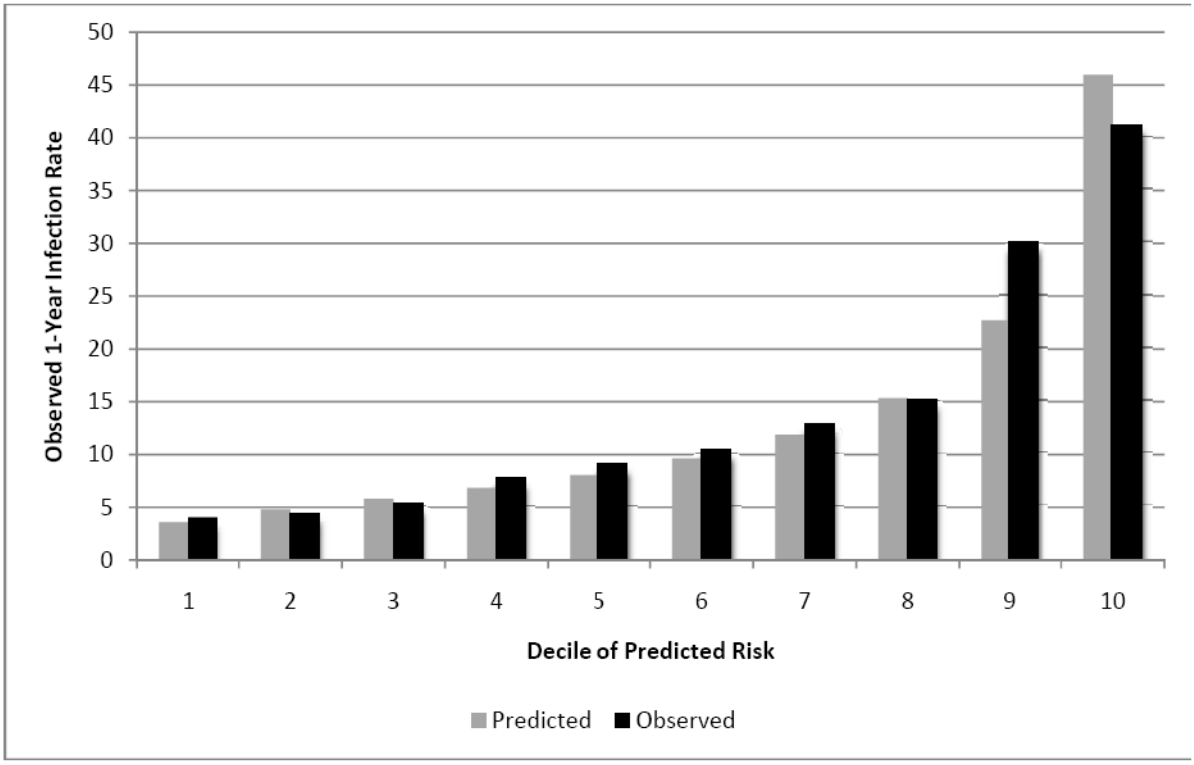
Significance and Innovation

- A person-specific infection risk score to predict the one year risk of hospitalized infection was derived and validated among RA patients initiating non-biologic DMARDs
- Using this risk score, predicted versus observed rates of serious infections were compared among new anti-TNF users. There was a constant rate difference of approximately 1–4 per 100 person-years associated with anti-TNF therapy regardless of whether the patient was a low or a 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. This comparative safety assessment has been minimally examined for infectious outcome except for opportunistic infections.



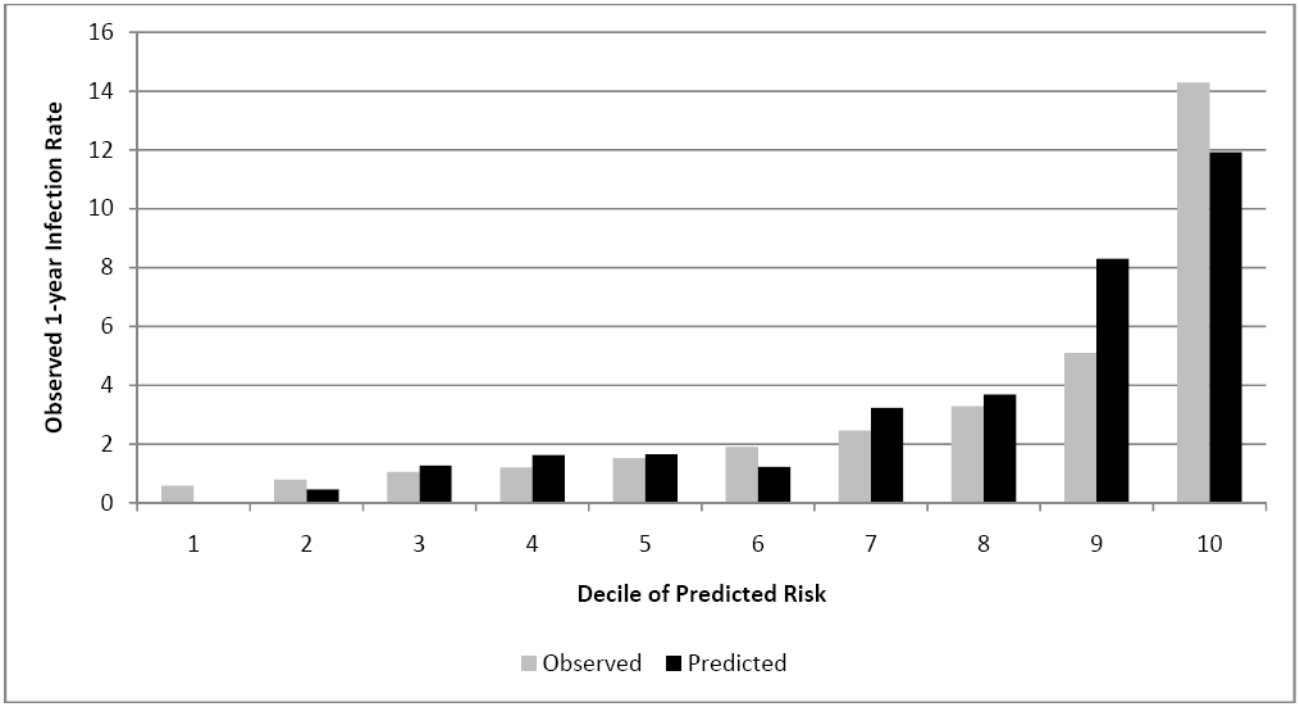


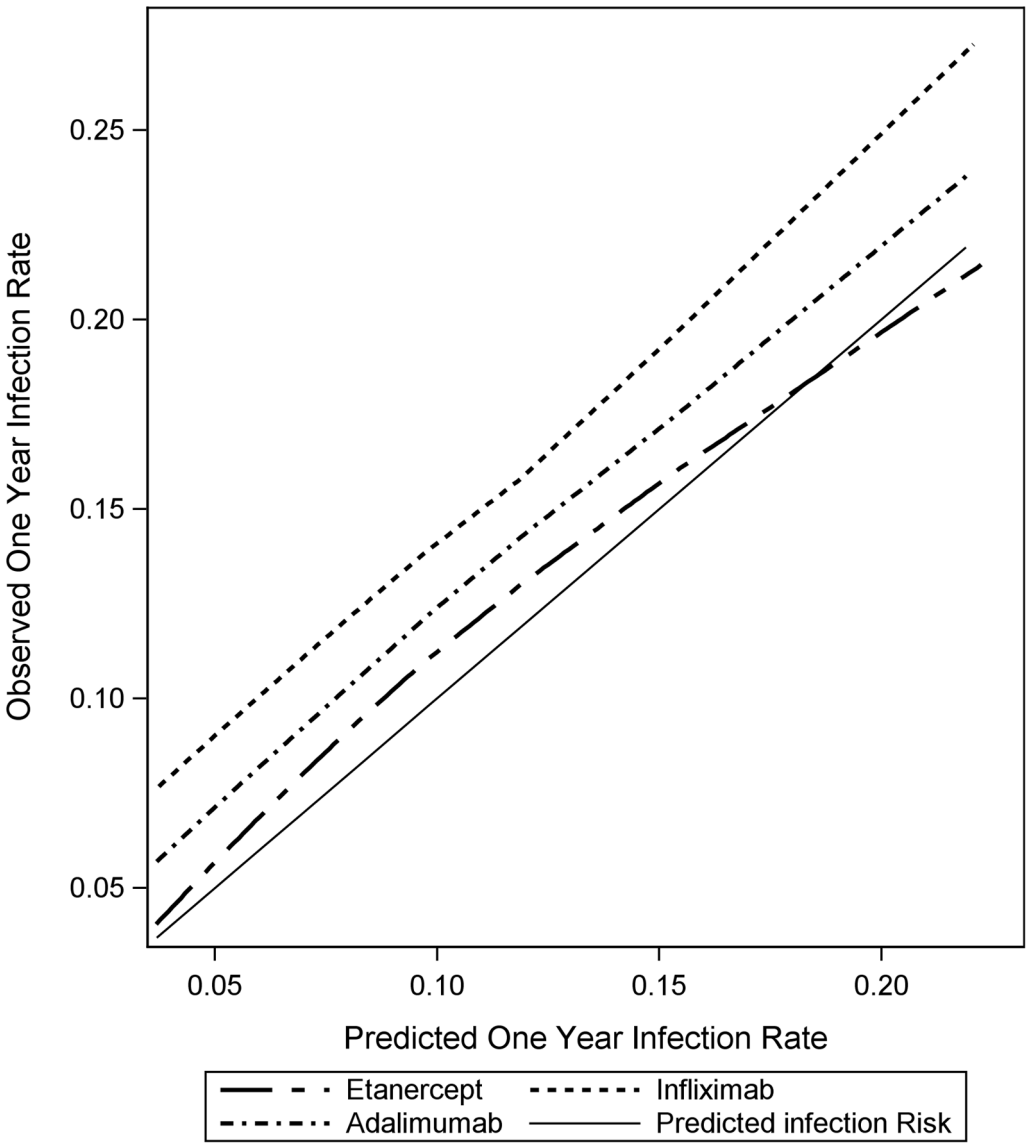
Figure 1.

Predicted versus Observed Mean Rate of Hospitalized Infection in RA patients initiating DMARDs* according to Decile of the Infection Risk Score for Governmentally insured RA patients (Figure 1a) and commercially insured RA patients (Figure 1b).

* new use of methotrexate, leflunomide, or sulfasalazine/hydroxychloroquine (with prior use of MTX in the previous year)

Infection risk score (black) vs. Observed Rate (mean 1-year rate from validation cohort derived from 200 bootstrap samples, grey)

The c index of the model for governmentally insured and commercially insured RA patients was 0.71 (0.69, 0.72) and 0.78 (0.75, 0.80), respectively



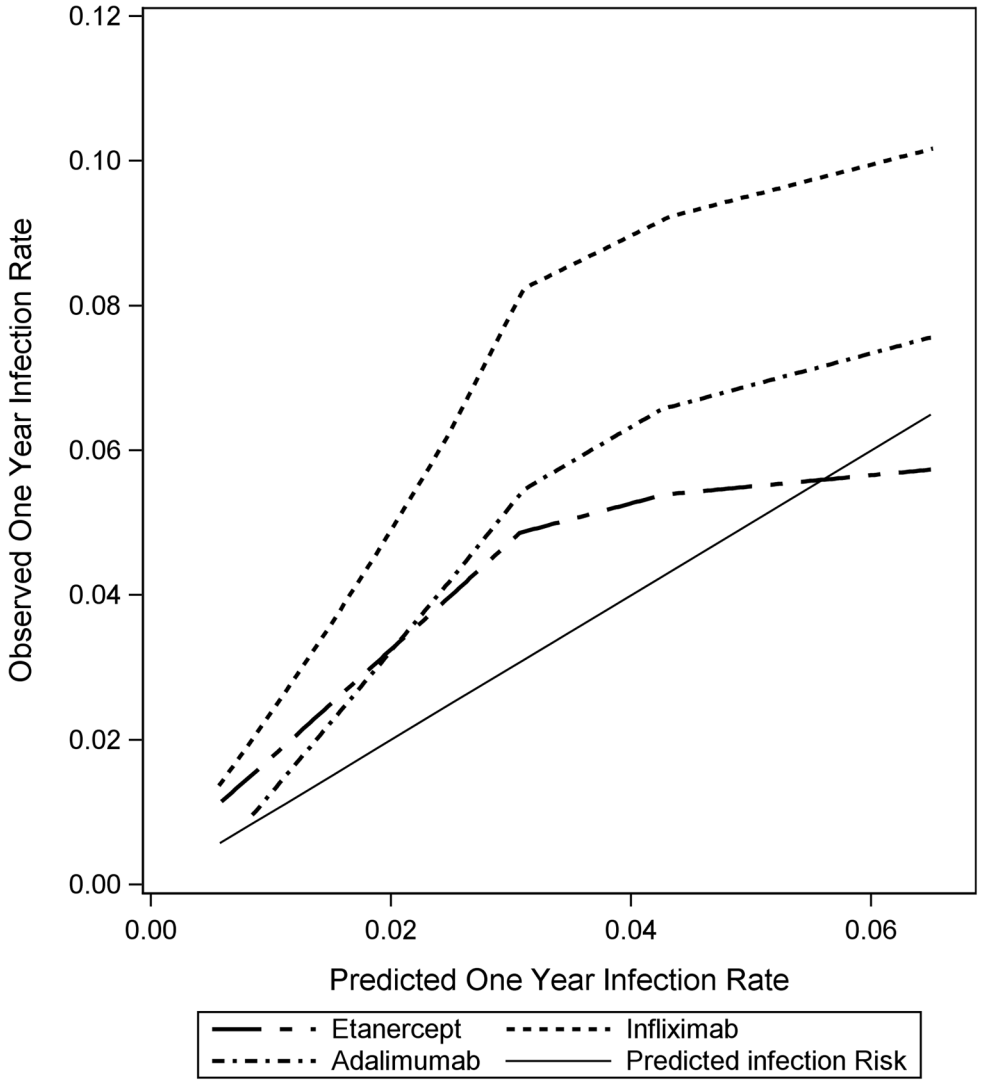


Figure 2.

Observed One-Year Infection Rate among Biologic Free* Infliximab, Etanercept and Adalimumab RA Patients enrolled in Medicare (Figure 2a) and Commercial Insurance (Figure 2b), by Predicted One-Year Infection Rate

* No biologic use in the 1 year prior to initiation

** All patients must have had an Infection Risk Score within the minimum and maximum range of each anti-TNF group; otherwise, they were excluded

Table 1

Characteristics of Governmental (Medicare + Medicaid) * and Commercially Insured ** Biologic-Free *** RA Patients Initiating Non-Biologic DMARDs or Anti-TNF Therapy

	Governmental Insurance		Commercial Insurance	
	N (%) or mean +− SD		N (%) or mean +− SD	
Treatment group and number of patients (treatment episodes)	**DMARD Users N = 14693 (14693)**	**Anti-TNF Users N = 6560 (7543)**	**DMARD Users N = 8823 (8823)**	**Anti-TNF Users N =5097 (5635)**
Age, 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 w/o complication	24.2	23.6	8.7	8.8
Diabetes w/ complication	5.027.7	5.3	1.6	1.7
CPD	16.2 6.6	27.3	12.7	12.7
Heart Failure	3.4	13.4	1.2	1.0
Malignancy	3.8	5.3	3.3	2.2
Angina diagnosis	0.2	3.1	0.6	0.6
Peptic ulcer disease	3.8	4.0	0.7	0.8
Hepatitis C	7.9	0.5	0.3	0.7
Renal Disease		3.4	1.4	1.4
Any Fracture	79.1	8.5	3.1	3.4
Hospitalized Infections	12.4			
None	8.5	80.3	93.7	93.7
1–2 episodes	1.8	11.5	4.1	4.0
3+ episodes		8.2	2.2	2.3
Ulcer		1.7	0.2	0.1
Medications, %	53.6			
Prednisone (mg/day)	27.4			
None	19.0	46.6	61.5	55.7
< 7.5mg	31.0	9.5	22.1	5.9
> 7.5mg	74.5	43.9	16.4	38.4
Bisphosphonates	5.1	42.7	8.0	10.0
Narcotics	62.7	77.3	57.0	58.6
Anti fungal medications	36.6	5.8	5.4	6.0
Hypertension medications	61.1	60.9	24.2	23.3
Antidepressant	65.4	38.8	26.4	29.6
Lipid screen	26.5	61.2	54.3	49.2
NSAID	0.7	64.2	51.0	49.9
Thiazide diuretics		25.9	15.0	14.8
Any Intra Articular Injection		0.8	0.2	0.1
Health Behaviors and Health Services Utilization, %				
PSA screen(men only)	49.5	51.2	28.1	23.5

	Governmental Insurance		Commercial Insurance	
	N (%) or mean +− SD		N (%) or mean +− SD	
Treatment group and number of patients (treatment episodes)	**DMARD Users N = 14693 (14693)**	**Anti-TNF Users N = 6560 (7543)**	**DMARD Users N = 8823 (8823)**	**Anti-TNF Users N =5097 (5635)**
Pap testing (women only)	12.7	13.5	36.2	34.0
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

NA = not applicable; PSA = prostate specific antigen; Pap = Papanicolaou

Note: a treatment episode is defined as new use of a medication with no prior use of that agent in the preceding one year

*Medicare dual eligible, restricted to age >= 65 at the start of follow-up

**restricted to age < 65 at the start of follow-up

***no biologic use in the 1 year prior to initiation

Table 2

Risk Factors for Infection Included in the Infection Risk Score for Governmentally and Commercially Insured RA Patients Initiating Non-biologic DMARDs[†]

Infection-Related Risk Factors	Medicare (n =14702)	Commercially Insured (n = 8892)
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Age <50		Referent
Age 50–59		1.46 (1.00,2.15)
Age 60–65		2.04 (1.17,3.56)
Age 65–69	Referent	
Age 70–74	1.29 (1.10,1.50)	
Age 75–79	1.61 (1.36,1.91)	
Age 80–84	1.80 (1.47,2.21)	
Age >85	2.11 (1.62,2.75)	
Women (referent to men)	0.75 (0.59,0.95)	
Comorbidities, %		
Diabetes w/o complication	1.14 (0.99,1.32)	2.24 (1.39,3.59)
Diabetes w/complications	1.74 (1.35,2.25)	4.21 (1.54,11.54)
CPD	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, <7.5mg	1.03 (0.89,1.18)	1.21 (0.76,1.92)
> 7.5mg	1.38 (1.19,1.62)	2.47 (1.63,3.720
Narcotics	1.24 (1.07,1.44)	1.46 (1.00,2.11)
Anti fungal 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)
Glucocorticoid Intra Articular Injection	1.53 (0.90,2.60)	
Bisphosphonates	0.87 (0.77,1.00)	2.19 (1.29,3.72)

Infection-Related Risk Factors	Medicare (n =14702)	Commercially Insured (n = 8892)
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Health Behaviors and Health Services Utilization		
PSA screen(man only)	0.73 (0.52,1.02)	
PAP 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 or more hospitalization	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)	

Note: 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 upon clinical interest and at least modest ($p < 0.15$) statistical association with hospitalized infection.

† New use of methotrexate, leflunomide, or sulfasalazine/hydroxychloroquine (with prior use of MTX in the previous year)

Appendix

ICD9 Code Diagnoses Represented in the Infection Risk Score

Condition	ICD-9 Code(s)
Diabetes w/o complication	250 – 250.3, 250.7
Diabetes w/complications	250.4 – 250.6
COPD	490 – 496, 500 – 505, 506.4
Heart Failure	428
Malignancy	140 – 172.9, 174 – 195.8, 200 – 208.9
Angina	411
Peptic ulcer disease	531 – 534.9
Hepatitis C	070.41, 070.44, 070.51, 070.54, V02.62
Dementia	290 – 290.9
Any Fracture	800 – 829.99, 733.1
Smoking	305.13, V15.82

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