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Predictors of Infection in Rheumatoid Arthritis Patients Using Anti-Tumor Necrosis Factor Agents

Tasia Liu
University of Rhode Island, tasialiu@my.uri.edu

PREDICTORS OF INFECTION IN RHEUMATOID ARTHRITIS PATIENTS USING ANTI-TUMOR NECROSIS FACTOR AGENTS

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TASIA LIU

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TASIA LIU

APPROVED:

Thesis Committee:

Major Professor Aisling Caffrey

Ashley Buchanan

Roberta King

Nasser H. Zawia
DEAN OF THE GRADUATE SCHOOL

UNIVERSITY OF RHODE ISLAND
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ABSTRACT

Background: Rheumatoid arthritis (RA) is an incurable autoimmune disease that can cause permanent joint damage and loss of function. Anti-tumor necrosis factor (anti-TNF) agents inhibit the function of tumor necrosis factor (TNF), which leads to a reduction in the progression of joint damage due to inflammation. However, an increased risk of serious infections in RA patients using anti-TNF agents has been observed in previous studies. This increased risk may be due to the immunologic disturbance of the RA disease process itself, the immunosuppressive properties of anti-rheumatic drug therapies, or co-existing risk factors for infection present in RA patients. Herein, our aim is to assess potential predictors of hospitalized infection in RA patients using anti-TNF agents.

Objective: Our objective is to determine if patients with RA who are prescribed the anti-TNF agents; adalimumab, etanercept, or infliximab, are at an increased risk of having a serious infection. In addition, we sought to identify potential predictors of an increased risk of infection in RA patients using anti-TNF agents.

Methods: A nested case-control study was conducted using de-identified data from the Clinformatics^{TM} DataMart (OptumInsight, Eden Prairie, MN), an administrative health claims database from a large national private insurer. An initial cohort of 78,657 patients with ≥1 RA diagnosis was identified. Patients were included from this initial cohort based on age, enrollment eligibility, number of RA diagnoses, exposure to an anti-TNF agent, and excluded based on certain comorbidities. A final RA cohort sample of 15,181 patients was formed. A follow-up period of 1 year was selected to analyze serious infections requiring hospitalization; these events were identified with a

comprehensive set of ICD-9 codes for serious infections requiring inpatient admission. Patients were classified as cases if they experienced a serious infection during the 1-year follow up. The final selected cases and controls were matched on a 1:1 ratio based on gender, region, and RA cohort entry date (quarter, year). A total of 155 cases and 155 controls were identified. Both univariable and multivariable conditional logistic regression models were built to produce a final multivariable predictive model.

Results: Among, RA patients using anti-TNF agents, those with recent prednisone use were 1.873 times more likely to have a hospitalized infection (95% confidence interval [CI] 1.015-3.458). Patients with comorbid diabetes were 2.963 times more likely to experience a hospitalized infection (95% CI 1.445-6.078) and patients with comorbid chronic obstructive pulmonary disease (COPD) were 9.233 times more likely to experience a hospitalized infection (95% CI 2.755-30.947). Lastly, patients with a previous history of infection were 8.984 times more likely to have a hospitalized infection (95% CI 1.895-42.595). No associations between anti-TNF agent (adalimumab, infliximab, or etanercept) or incident/prevalent anti-TNF use and hospitalized infection were observed.

Conclusion: The use of specific anti-TNF agents was not independently associated with an increased risk of hospitalized infection in RA patients. Predictors associated with hospitalized infection in RA patients using anti-TNF agents included recent prednisone use, comorbid diabetes, comorbid COPD, and previous history of infection.

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PREFACE

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CHAPTER 1

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the chronic inflammation of synovial joints causing persistent pain and stiffness that can eventually result in joint deformities and loss of function.[1] Given the debilitating nature of RA, the disease poses a significant negative impact on health-related quality of life.[2,3] In 2005, an estimated 1.3 million (0.6%) adults had RA in the United States (US).[4] There is no cure available for RA, but the condition can be managed to slow down the progression of disease and improve a patient's quality of life. Current treatment options for RA include non-steroidal anti-inflammatory drugs (NSAIDs), traditional disease-modifying anti-rheumatic drugs (DMARDs), and biologic DMARDs. The type of treatment used depends on a patient's disease activity, signs and symptoms, and prognosis. The current treatment model for RA focuses on an early, aggressive combination therapy approach by prescribing a combination of multiple drugs early on in order to achieve adequate disease control as quickly as possible.[5]

Biologic DMARDs, particularly anti-tumor necrosis factor (anti-TNF) drugs have emerged as important agents in the treatment of RA, especially in patients who have failed to respond to traditional DMARDs alone. Anti-TNF medications approved by the US Food and Drug Administration (FDA) for a number of conditions including rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis,

psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis.[6] The introduction of anti-TNF drugs beginning in the late 1990s revolutionized the treatment of rheumatoid arthritis (RA) as they have been shown to be very effective at reducing inflammation in RA patients.[7-9]

Tumor necrosis factor (TNF) plays an important role in host cell defense as a pro-inflammatory cytokine involved in systemic inflammation.[10] This inflammatory response against harmful bacteria and viruses is controlled and regulated by the body under normal conditions. In patients with RA, macrophages overproduce TNF leading to inflammation of the joints. Anti-TNF agents inhibit the function of TNF by preventing TNF from binding to its receptor, which reduces the progression of joint damage due to inflammation.[10,11]

An uncommon, yet significant side effect associated with anti-TNF drug use is the increased risk of serious infections.[12,14-16] The prescribing information for the anti-TNF agents; adalimumab, etanercept, and infliximab contains black box warnings ordered by the FDA indicating the increased risk of serious infection leading to hospitalization or death and recommending discontinued use if a patient develops a serious infection.[17-19] This increased risk of infection may be due to the immunologic disturbance of the RA disease process, the immunosuppressive properties of anti-rheumatic drug therapies, or co-existing risk factors for infection present in RA patients. Most likely, this increased risk of infection is due to a combination of these different factors.[12-15]

A retrospective longitudinal cohort study published by Doran et al[20] in 2002 compared infection rates in a group of patients with RA with those in a group of

individuals without RA. The study reported results from a cohort of Rochester, Minnesota residents who were first diagnosed as having RA between 1955 and 1994. Study subjects were followed until death, migration from the area, or study end (January 1, 2000), whichever came first. Among 609 patients with incident RA in 1955-1994, 290 (47.6%) experienced ≥1 serious infection. Infections requiring hospitalization were significantly more frequent in RA patients (9.57/100 person-years) than in non-RA study subjects (5.09/100 person-years) with a rate ratio of 1.88 (95% confidence interval [CI] 1.71-2.07). In other words, the researchers found that the risk of developing a serious infection requiring hospitalization in patients with RA was estimated to be nearly two-fold in comparison with non-RA patients. As this study occurred before anti-TNF agents were widely available for the treatment of RA, the increased risk of infection in RA patients was well established before the introduction of anti-TNF agents to the RA drug market.

Research to better understand the risk factors associated with the increased rate of hospitalized infection in RA patients using anti-TNF agents remains limited, particularly among patient populations within the US. The lack of studies focusing on risk factors establishes a need for further research to identify potential predictors of hospitalized infection in this patient population using medications which can increase their risk of infection.

Therefore, the objective of this study was to determine whether specific anti-TNF agents, adalimumab, etanercept, or infliximab, increased the risk of hospitalized infection. A secondary objective was to identify potential predictors for hospitalized infection in RA patients using anti-TNF agents. These findings will help inform

clinicians and patients about factors that may affect the development of serious infections.

The hypothesis for this study is that the odds of hospitalized infection among RA patients using anti-TNF agents will be greater in patients with older ages, corticosteroid use, disease modifying anti-rheumatic drug (DMARD) use, and comorbidities such as diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disorder.

CHAPTER 2

REVIEW OF LITERATURE

Although numerous studies have explored the association between anti-TNF use and an increased risk of infection, fewer studies in comparison have focused on identifying additional potential predictors of hospitalized infection in RA patients treated with these medications.

Studies were eligible for inclusion into the literature review based on several broad criteria. We searched for studies using PubMed, the Cochrane databases, and Google Scholar and identified studies published from 2007 to 2013. First, the reviewed studies had to have a study cohort comprised of only RA patients defined as having ≥1 RA diagnosis. Second, exposures of interest had to include the anti-TNF agents, adalimumab, etanercept, and infliximab. Studies that evaluated newer anti-TNF agents such as golimumab and certolizumab pegol were not included into our literature review. And lastly, the outcome of interest had to include, but was not limited to serious infection requiring hospitalization. **Appendix 1** lists the selected studies with further details on study design, patient population, inclusion and exclusion criteria, exposure and outcome, and significant predictors.

A retrospective cohort study by Curtis et al[12] published in 2007 used data from the medical and pharmacy administrative claims of a large US health care organization. The objective of this study was to evaluate the risk of serious bacterial infections in RA patients using anti-TNF agents and traditional DMARDs alone.

Researchers found that the adjusted hazard ratio (HR) of hospitalized bacterial infection among patients who received anti-TNF drugs was 1.9 (95% confidence interval [CI] 1.3–2.8) compared with patients who received methotrexate only. In other words, the risk of hospitalized bacterial infection was approximately 2-fold higher among patients receiving anti-TNF agents versus patients receiving methotrexate alone. Significant predictors of infection included anti-TNF use, older age, number of physician visits, prior infection, concomitant prednisone use, and presence of comorbidities, including chronic obstructive pulmonary disease/asthma, diabetes mellitus, and kidney disease.

A retrospective cohort study by Favalli et al[21] published in 2009 used data from the regional population-based Lombardy Rheumatology Network (LORHEN) registry consisting of RA patients using anti-TNF agents from four major Rheumatology Units in Lombardy, Italy. The objective of the study was to estimate the incidence of serious infections in the patients treated with anti-TNF agents and identify significant predictors of infection. The researchers found that 6.9% of patients in the eligible cohort experienced a serious infection requiring hospitalization and/or intravenous antibiotic therapy with an overall incidence rate of 3.59/100 patient-years (95% CI 2.77–4.41). Significant predictors of infection included age (per 1 year), concomitant prednisone use, and erythrocyte sedimentation rate (ESR).

A retrospective cohort study by Atzeni et al[22] published in 2012 used data from the nationwide Gruppo Italiano Studio Early Arthritis (GISEA) registry, which registers and monitors rheumatic patients treated with biological drugs at hospital and community-based rheumatology units throughout Italy. The objective of the study was

to assess the risk of serious infections in RA patients using anti-TNF therapy and identify potential risk factors. The researchers found that 6.36% of patients over a follow-up time of 9 years in the eligible cohort experienced a serious infection requiring hospitalization or intravenous antibiotic therapy with an overall incidence rate of 3.18/100 patient-years (95% CI 2.52–3.83). Significant predictors of infection included corticosteroid therapy, concomitant DMARD therapy, and age at the start of anti-TNF treatment.

A nested case-control study by Widdifield et al[23] published in 2013 used data from the Ontario Health Insurance Plan (OHIP) Database, an administrative claims database comprised of patients in Ontario, Canada. The objective of the study was to identify the risk of infection in a cohort of seniors with RA using anti-TNF agents in the OHIP database and identify potential risk factors for infection. The researchers found that 23.91% of patients over a follow-up time of 12 years in the eligible cohort experienced a serious infection requiring hospitalization or an ER visit for an incidence rate of 4.64 events/100 patient years (95% CI not reported). Significant predictors of infection included rural residence, diabetes mellitus, chronic lung disease, renal disease, glucocorticoid use ≤5 mg/day, glucocorticoid use ≥20 mg/day, methotrexate use ≤10 mg/day, methotrexate use >10 mg/day, anti-TNF use, extra articular features of RA, joint replacements, and history of previous infection.

A retrospective cohort study by van Dartel[24] et al published in 2013 used data from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. The objective of the study was to identify predictors of the increased risk of serious infections in RA patients treated with anti-TNF agents. Researchers found that 6.3% of patients over a

follow-up time of 5 years in the eligible cohort developed a serious infection requiring hospitalization and/or intravenous antibiotic therapy. The incidence rate in the first year after the initiation of anti-TNF therapy was 4.57/100 patient-years and 2.91/100 patient-years over 5 years (95% CI not reported). Significant predictors of infection included older age, corticosteroid use, visual analogue scale (VAS) pain, Health Assessment Questionnaire (HAQ), tender joint count 28 joints (TJC28), and presence of comorbidities.

From a review of the literature, the majority of studies that investigate possible risk factors for infection in RA patients using anti-TNF agents have been performed using data from rheumatic disease registries and healthcare databases from outside of the United States. The one US study by Curtis et al[12], included patients with and without anti-TNF use. Significant predictors of infection that were common across the studies reviewed included increased age, corticosteroid use, DMARD use, and presence of comorbidities such as diabetes, chronic kidney disease, and chronic obstructive pulmonary disorder (COPD).

The objective of this study was to assess risk factors for serious infections requiring hospitalization in RA patients using anti-TNF agents. This study will provide clinicians and RA patients with more knowledge on which factors are predictive of an increased risk of infection which may help reduce and prevent such infections. Furthermore, the use of a large, national administrative claims database representative of the privately insured population in the United States will produce more generalizable results on potential risk factors for infection among patients with RA in the United States.

CHAPTER 3

METHODOLOGY

Study Design and RA Cohort Definition

A nested case-control study was conducted using data from the Clinformatics™ DataMart (OptumInsight, Eden Prairie, MN), an administrative health claims database from a large national private insurer. The database contains de-identified patient level data across multiple categories including medical claims, pharmacy claims, and administrative data. We selected a nested case-control design because it is efficient for the study of rare outcomes and good for assessing multiple exposures. The outcome of interest in this study, hospitalized infection, is relatively rare with rates of infection ranging from 6-7% during extended follow-up time periods.[22,24] Data from the study time period of January 1, 2010 to December 31, 2013 was used in the analyses.

For inclusion into the RA cohort, both cases and controls had to be 18 to 63 years old at the time of their entry into the RA cohort (for a timeline of the RA cohort, please see **Figure 1**). Both cases and controls had to have ≥2 RA diagnoses (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code for RA of 714.x) separated by >7 days and occurring within 1 year of each other. Patients also had to have continuous enrollment for ≥2 years. More specifically, patients had to be continuously enrolled for the 12-months before the first RA diagnosis and the 12-months after the first RA diagnosis. The RA cohort entry date is defined as the date of the first RA diagnosis in which all the predefined RA

cohort criteria were met. The reasoning for requiring continuous enrollment in the 12-months prior to the first RA diagnosis is to establish a look-back period for the assessment of covariates such as a previous history of infection. Patients were followed starting from the cohort entry date until 12-months or until the outcome of interest occurred, whichever event came first.

Lastly, both cases and controls were required to have ≥1 medical or prescription claim for an anti-TNF agent (adalimumab, etanercept, or infliximab) occurring after the RA cohort entry date and before the outcome of interest. This inclusion criteria was applied in order to increase our specificity of RA case ascertainment and to establish temporality that both cases and controls were exposed to an anti-TNF agent prior to the outcome of interest (hospitalized infection). As controls do not experience the outcome of interest, each matched control was assigned the same index date (defined as the date of the first hospitalized infection in cases) as its matched case. Further details on identification of cases and controls are presented in the next section.

Patients were excluded for loss of coverage or inpatient death occurring ≤12 months after the cohort entry date. Patients were also excluded if they had a diagnosis ±12-months of the cohort entry date for another condition for which adalimumab, etanercept, and infliximab are approved, including Crohn's disease, ulcerative colitis, psoriatic arthritis, plaque psoriasis, or ankylosing spondylitis.[25] Patients were also excluded if they had a diagnosis ± 12-months of the cohort entry date for malignant neoplasm[26] (for ICD-9-CM codes of exclusion criteria, see **Appendix 2**). The previously mentioned exclusion criteria for comorbidities was introduced to increase the homogeneity of the sample because RA patients with other autoimmune and

inflammatory conditions may have different infection risk profiles and infection-related risk factors.

Identification of Cases and Controls

Cases and controls were derived from the aforementioned RA cohort (for a timeline of the nested case-control design, please see **Figure 2**). Cases were defined as patients who had an inpatient hospital admission code in any position for infection in the 12-months following the cohort entry date. The outcome of interest for cases was restricted to only the earliest hospitalized infection. Outcome events were identified using a comprehensive set of ICD-9 codes developed as part of a systematic literature review and two validation studies to identify serious infections in RA patients (for ICD-9-CM codes, see **Appendix 3**). This particular infection algorithm has demonstrated positive predictive values of ≥80%.[27] For each case, an index date was assigned corresponding to the date of the inpatient hospital admission.

Controls included those not experiencing a hospitalized infection in the 12-months following the cohort entry date. Controls were randomly matched (without replacement) to cases on a 1:1 ratio based on gender, geographic region, and cohort entry date (quarter, year). Since the controls do not experience the outcome of interest, hospitalized infection, each matched control was assigned the same index date as its matched case.

Drug Exposure Determination and Potential Predictors

Cases and controls were considered exposed to an anti-TNF agent if they had ≥1 pharmacy or medical claim for adalimumab, etanercept, or infliximab in the 90-days prior to the index date. Patients could be exposed to ≥1 anti-TNF agent during this 90-

day exposure risk window. The self-injectable drugs adalimumab and etanercept were identified based on pharmacy claims for prescription fills (see **Appendix 4**). Adalimumab and etanercept were also identified based on medical claims considering the fact that when adalimumab and etanercept are first prescribed to a patient, the first injection is administered as part of a training session for the patient in an office setting under the supervision of a health care professional.[17,18] The exposure risk window for adalimumab and etanercept will need to capture the possibility of the first dose being administered in the office in addition to prescription fills. The infused drug infliximab was identified based on medical claims, specifically the common procedure codes (CPT) 96413 and 96415 for the 1st and 2nd hour of infusion, respectively.[28]

Potential predictors were selected based on general risk factors associated with the etiology of RA and the relevant published literature[12,21-24]. Although previous studies have shown an increased risk of infection correlated with disease severity measures such as disease activity score 28 (DAS28), health assessment questionnaire (HAQ), and visual analogue scale (VAS), these measures of disease activity were not available from the Clinformatics™ DataMart (OptumInsight, Eden Prairie, MN). Gender and geographic region (Northeast, Midwest, South, and West) were selected as matching variables, therefore they were not assessed as risk factors. To ascertain potential predictors of hospitalized infection in RA patients using anti-TNF drugs, the following covariates were collected for each case and control:

- Age
- Number of rheumatologist visits from RA cohort entry date to index date

- Previous infection: hospitalized infection occurring ≤12-months prior to the RA cohort entry date
- Joint replacement ≤360 days prior to index date
- Exposure to specific anti-TNF medications: adalimumab, etanercept, and/or infliximab, ≤90 days prior to index date
- Exposure to disease modifying anti-rheumatic drugs (DMARDs), or corticosteroids: methotrexate, azathioprine, leflunomide, hydroxychloroquine, sulfasalazine, prednisone, ≤90 days prior to index date
- Comorbidities: diabetes, chronic kidney disease (CKD), obstructive pulmonary disorder (COPD), ≤90 days prior to index date
- Prevalent or incident user of anti-TNF drug:
    - Prevalent (new) user: ≥1 claim for exposed anti-TNF drug(s) occurring between cohort entry date and 90-day exposure period
    - Incident (continuing) user: 0 claims for exposed anti-TNF drug(s) occurring between cohort entry date and 90-day exposure period

Statistical Analysis

Differences in the distribution of covariates among cases and controls was assessed using Chi-squared tests for categorical variables and two-sample t-tests for continuous variables. Conditional logistic regression was performed to assess the relationship between the dependent variable, the first hospitalized infection, with the independent risk factors described above. Multivariable conditional logistic regression was performed with inclusion of variables with a p-value ≤0.20 in the univariable models. A manual, backward, step-wise elimination was carried out to remove

variables with a Wald p-value >0.05 to produce a final multivariable model of variables significantly associated with the dependent variable. To determine goodness of fit, Akaike information criteria (AIC) values were compared between competing models and a Hosmer-Lemeshow test was used to assess the final model fit. Collinearity was assessed in the final model to determine if any of the independent variables were highly correlated with one another. A variance inflation factor (VIF) ≥10 and/or a tolerance (TOL) value ≤0.10 would indicate variables with possible collinearity.[29] The odds ratios (OR) for hospitalized infection risk for each risk factor was calculated with 95% confidence intervals and a p-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS® Version 9.4. (Cary, NC).

CHAPTER 4

FINDINGS

Study Population Characteristics

There were 176,745 patients initially identified as having ≥1 RA diagnosis during the study time frame of January 1, 2010 to December 31, 2013 (for study population flow chart, see **Figure 3**). All RA patients initially identified were age 18-63 years old. All RA patients initially identified also had ≥2 RA diagnoses separated by >7 days and occurring within 1 year of each other. Therefore, no patients were excluded based on inclusion criteria involving age or RA diagnoses. We then excluded patients who did not have continuous enrollment in the 12-months before their first RA diagnosis and the 12-months after their first RA diagnosis (N=97,752). Next, patients with a diagnosis ± 12-months of the RA cohort entry date for Crohn's disease, ulcerative colitis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, or malignant neoplasm were excluded (N=336). We then excluded patients without ≥1 prescription or medical claim for an anti-TNF agent occurring in the 12-months after the RA cohort entry date (n=63,476) resulting in a final eligible RA cohort of 15,181 patients.

Next, we identified cases as the patients who experienced a hospitalized infection occurring between the patient's RA cohort entry date and the end of the 1-year follow up period. A total of 255 eligible cases was identified. Next, we excluded eligible cases and controls who did not have ≥1 prescription or medical claim for an anti-TNF agent occurring between the RA cohort entry date and the index date (n=965). After

all inclusion and exclusion criteria were applied, one control was matched to each case according to the matching variables gender, region, and cohort entry date (quarter, year). We were able to identify 155 cases matched on a 1:1 ratio to 155 controls.

The demographic and clinical characteristics of cases and control are presented in **Table 1**. Cases and controls did not differ significantly in regards to age (p=0.6877) with both cases and controls having a mean age of approximately 45 years old. The majority of cases (56.13%) and controls (62.58%) had ≥2 rheumatologist visits between their RA cohort entry date and their index date, and this difference was not statistically significant (p=0.5048). Both cases and controls were mostly female (75.48%) and from the South (50.32%). Adalimumab use (p=0.6556) and infliximab use (p=0.4030) did not differ significantly between cases and controls. However, etanercept use differed significantly between cases and controls (15.48% cases, 25.81% controls; p=0.0248). Prednisone use was significantly higher in cases compared with controls (31.61% cases, 21.29% controls; p=0.0394). Cases had a significantly higher frequency of comorbid conditions including diabetes (30.32% cases, 10.97% controls; p=<0.0001) and COPD (25.16% cases, 3.23% controls; p=<0.0001). Cases also experienced a significantly higher frequency of previous infection compared with controls (10.97% cases, 1.29% controls; p=0.0004).

Univariable Analysis

In univariable logistic regression, we identified covariates having a statistically significant association with the occurrence of hospitalized infection. Results of the univariable analysis of potential risk factors are presented in **Table 2**. Covariates with a p-value ≤0.20 were considered for building multivariable models. Based on

univariable comparison of cases and controls; age, etanercept use, methotrexate use, prednisone use, comorbid diabetes, comorbid chronic kidney disease, comorbid COPD, joint replacement, and previous history of infection were considered for the multivariable model.

Univariable analysis of incident user and prevalent user of anti-TNF agents was not statistically significant (p=0.3551). However, the covariate, incident user, was forced into the initial multivariate model to assess whether incident user could be used to create an interaction term with etanercept use in the event that both main effects were statistically significant in multivariable analysis. A significant interaction between incident user and etanercept use would indicate that there is evidence that hospitalized infection in patients using etanercept is related to whether the patient is an incident user of etanercept.

Multivariable Analysis

Multivariable conditional logistic regression models were built to examine the association between anti-TNF drug use and the occurrence of serious infection requiring hospitalization. Results of the final model are presented in **Table 3**.

RA patients with recent prednisone use were 1.873 times more likely to have a hospitalized infection (95% CI 1.015-3.458). Patients with comorbid diabetes were 2.963 times more likely to experience a hospitalized infection (95% CI 1.445-6.078) and patients with comorbid COPD were 9.233 times more likely to experience a hospitalized infection (95% CI 2.755-30.947). Lastly, patients with a previous history of infection were 8.984 times more likely to have a hospitalized infection (95% CI 1.895-42.595).

Collinearity was assessed in the final model to determine if any of the independent variables were highly correlated with one another. The variance inflation factors (VIF) were all well under 10 and the tolerance (TOL) values were all greater than 0.10. Therefore, there was no evidence of collinearity based on VIF and TOL. Lastly, a Hosmer-Lemeshow test was performed on the final model to determine if the model was an adequate fit for the data. The Hosmer-Lemeshow test produced a p-value of 0.6925, which is greater than 0.05. Therefore, there was no evidence that our model fits inadequately based on this test.

Discussion

Anti-TNF agents are effective for the treatment of RA, but may increase the risk for serious infections. The FDA requires manufacturers of anti-TNF agents to include black box warnings alerting health care professionals and patients of the risk of serious infections leading to hospitalization or death when using anti-TNF agents.[17-19] A number of randomized clinical trials have demonstrated this increased risk. In a meta-analysis of 44 randomized, double-blind, controlled trials of patients with RA that evaluated anti-TNF use, anti-TNF agents as a group was associated with a higher risk of serious infection (Odds ratio [OR] 1.42, 95% confidence interval [CI] 1.13-1.78) compared with placebo and traditional disease-modifying anti-rheumatic drug treatments (DMARDs).[30]

Based on previous studies in other patient populations, we hypothesized that in RA patients using anti-TNF agents, the odds of hospitalized infection would be greater in patients with older ages, corticosteroid use, disease modifying anti-rheumatic drug

(DMARD) use, and comorbidities such as diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disorder (COPD).

We assessed the association between anti-TNF use in RA patients and the increased risk of hospitalized infections in a large national privately insured population. Significant predictors of hospitalized infection in RA patients using anti-TNF agents were prednisone use, comorbid diabetes, comorbid COPD, and previous history of infection.

In relation to existing research, our findings are in agreement with studies that report an increased risk of serious infections in RA patients with prednisone use, diabetes, COPD, and previous history of infection.

In a retrospective cohort study by Favalli et al[21] to assess the incidence of serious infection in patients treated with anti-TNF agents, significant predictors of an increased risk of infection included prednisone use (Hazard ratio [HR] 2.89, 95% CI 1.12–7.48). Similarly, Atzeni et al[22] conducted a retrospective cohort study to evaluate the risk of serious infection in RA patients using anti-TNF agents and also found that the use of corticosteroids (HR 1.63, 95% CI 1.01-2.64) was a significant predictor of an increased risk of infection. In a nested case-control conducted by Widdifield et al[23] comparing senior RA patients with incident serious infection to matched controls, significant predictors of an increased risk of infection were chronic lung disease (OR 1.31, 95% CI 1.25-1.36), previous history of infection (OR 1.51, 95% CI 1.45-1.57), and prednisone use (OR 3.96 at low doses, 95% CI 3.67-4.27; OR 7.57 at high doses, 95% CI 6.87-8.34). In a retrospective cohort study by van Dartel et al[24] to identify potential predictors of an increased risk of infection in RA patients using anti-TNF

agents, significant predictors of an increased risk of infection were corticosteroid use (HR 1.54, 95% CI 1.08-2.20) and the presence of comorbidities (diabetes, COPD, and cardiovascular disease were assessed as a single variable) (HR 1.31, 95% CI 0.98-1.175).

We did not identify an independent association between the increased risk of hospitalized infection and the use of specific anti-TNF agents. There is not a consistent consensus as to whether the risk of serious infections differs between adalimumab, etanercept, and infliximab with earlier studies reporting conflicting results. In studies that have assessed potential differences in risk between anti-TNF agents, Favalli et al[21] reported no statistically significant difference in risk between adalimumab, etanercept, or infliximab. On the contrary, Atzeni et al[22] demonstrated that the use of infliximab (HR 4.20, 95% CI 2.71-8.91) or adalimumab (HR 2.22, 95% CI 1.12-4.42) when compared to the use of etanercept were strong and significant predictors of infection.

Demographic and patient characteristics unique to our RA cohort, as well as other limitations of the study design may be contributing factors as to why our results differed from previous studies. In regards to increased age as a potential predictor, we were unable to find an association between an increased risk of serious infection and older age. Previous studies that evaluated age as a continuous variable like our study have shown patients with increased age are at a higher risk of serious infection with an adjusted hazard ratio of approximately 1.03.[21,22] Another study that evaluated age as a categorical variable showed patients >65 years old were at an approximately two-fold higher risk of experiencing a serious infection compared to patients <55 years old.[24] A

potential reason as to why we were unable to find an association between the occurrence of serious infection and increased age may be attributed to the younger and narrower age range of our study sample, which only included patients aged 44-48 with an average age of approximately 45 years old in both our case and control groups.

Although our final eligible RA cohort was relatively large, a fairly small number of hospitalized infection events (1.7%) were identified resulting in a smaller sample size for our nested case-control design. Our smaller sample size contributed to wide confidence intervals of the effect estimates from our final multivariable model and may have limited our power to detect an association between anti-TNF use and additional potential predictors. If we were able to identify a substantially larger sample size, we could have potentially identified more predictors, but the strength of the association related to many additional predictors may be weaker. Our study was able to identify strong and significant predictors of infection, particularly in patients with comorbid COPD and previous history of infection despite our small sample size and resultant wide confidence intervals.

In addition, the nested case-control design means that causality cannot be explicitly inferred between anti-TNF use and hospitalized infection as not all relevant risk factors are captured and recorded within the dataset. Therefore, it is not possible to measure and control for all factors that may have influenced the occurrence of hospitalized infection.

Furthermore, previous studies have found measures of RA disease severity to be significant predictors of hospitalized infection in patients using anti-TNF drugs. However, the Clinformatics™ DataMart does not directly capture indicators of disease

severity. We included proxies of disease severity as potential predictors in our analyses, such as the number of rheumatologist clinic visits from RA cohort entry date to index date, prednisone use, and presence of comorbidities. In addition, there is no evidence that confounding by indication is a concern according to the type of anti-TNF agent. The 2015 American College of Rheumatology (ACR) recommendations do not indicate a particular order of preference when prescribing an anti-TNF agent to a patient based on disease severity.[31] Future research may be directed towards further analyses using disease risk scores as a stronger proxy for disease severity.

Strengths of our study include the use of validated ICD-9 codes with proven high positive predictive values for disease to identify cases of hospitalized infection in administrative data, which may reduce potential misclassification bias. In addition, the use of a large privately insured population allows for more generalizable results for RA patients using anti-TNF agents in the US as opposed to studies that use data sources outside of the US. However, this also means that the results cannot be extrapolated towards patient populations beyond the privately insured. Furthermore, our results are not representative of older patient populations like those represented in Medicare. Our results are only generalizable to a population representative of our final patient sample such as being predominantly female, younger, from the South, and privately insured RA patients in the United States when most previous studies have analyzed populations outside of the US.

CHAPTER 5

CONCLUSION

Anti-TNF agents are known to inhibit the function of tumor necrosis factor, which can lead to a reduction of joint damage and inflammation in RA patients using these agents. However, serious infections have been reported in patients using anti-TNF drugs.

In our patient cohort, we were unable to identify a significant association between the increased risk of hospitalized infection and specific anti-TNF use in RA patients. Significant predictors of hospitalized infection in RA patients using anti-TNF agents included recent prednisone use, diabetes, COPD, and previous history of infection. The impact of these findings suggest that careful monitoring of these specific patient populations may be important in reducing the occurrence of hospitalized infection among patients using anti-TNF agents.

TABLES

TABLE 1: Demographic and clinical characteristics of RA patients – cases and controls (N=310)

Variable	Cases n=155 Frequency (%)	Controls n=155 Frequency (%)	p-value
Age, mean ± SD	45.51 ± 1.13	45.56 ± 1.13	0.6877
Male gender	38 (24.52)	38 (24.52)	1.0000
Number of rheumatologist visits from RA cohort entry date to index date:			
0 visit	28 (18.06)	23 (14.84)	0.5048
1 visit	40 (25.81)	35 (22.58)	
≥ 2 visits	87 (56.13)	97 (62.58)	
Region:			
Northeast	9 (5.81)	9 (5.81)	1.0000
Midwest	39 (25.16)	39 (25.16)	
South	78 (50.32)	78 (50.32)	
West	29 (18.71)	29 (18.71)	
Anti-TNF drug exposure 90 days prior to index date			
Adalimumab	26 (16.77)	29 (18.71)	0.6556
Etanercept	24 (15.48)	40 (25.81)	0.0248
Infliximab	57 (36.77)	50 (32.26)	0.4030
Other drug exposure 90 days prior to index date			
Methotrexate	38 (24.52)	51 (32.90)	0.1027
Prednisone	49 (31.61)	33 (21.29)	0.0394
Azathioprine	1 (0.65)	2 (1.29)	0.5618
Leflunomide	5 (3.23)	5 (3.23)	1.0000
Hydroxychloroquine	17 (10.97)	15 (9.68)	0.7089
Sulfasalazine	5 (3.23)	8 (2.58)	0.3953
Comorbidities			
Diabetes mellitus (90 days prior to index date)	47 (30.32)	17 (10.97)	<.0001
Chronic kidney disease (90 days prior to index date)	10 (6.45)	5 (3.23)	0.1857
Chronic obstructive pulmonary disorder (90 days prior to index date)	39 (25.16)	5 (3.23)	<.0001

TABLE 1 (continued): Demographic and clinical characteristics of RA patients – cases and controls (N=310)

Variable	Cases n=155 Frequency (%)	Controls n=155 Frequency (%)	p-value
Joint replacement (360 days prior to index date)	7 (4.52)	2 (1.29)	0.0908
Previous history of infection (hospitalized infection 12 months prior to cohort entry date)	17 (10.97)	2 (1.29)	0.0004
Prevalent or incident user of anti-TNF drug			
Incident (0 claims for exposed anti-TNF drug(s) between cohort entry date and 90-day exposure period)	82 (52.90)	75 (48.39)	0.4265
Prevalent (≥1 claim for exposed anti-TNF drug(s) between cohort entry date and 90-day exposure period)	73 (47.10)	80 (51.61)	0.4265

TABLE 2: Univariable logistic regression analysis of covariates

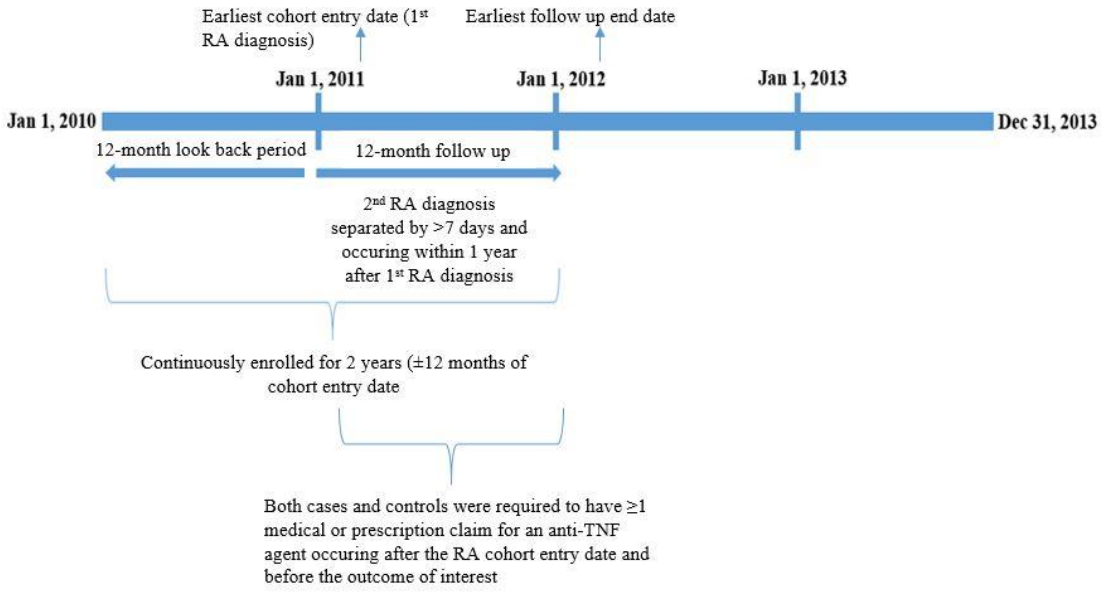
Variable	Univariable Model Odds Ratio	95% Confidence Interval (CI)	Unadjusted p-value
Age	0.111	0.014-0.877	0.0371
Number of rheumatologist visits from RA cohort entry date to index date (ref=0)			
1 visit	1.063	0.487-2.321	0.8783
≥ 2 visits	0.695	0.365-1.323	0.2682
Anti-TNF drug exposure 90 days prior to index date			
Adalimumab	0.870	0.478-1.583	0.6476
Etanercept	0.500	0.274-0.911	0.0236
Infliximab	1.269	0.759-2.122	0.3633
Other drug exposure 90 days prior to index date			
Methotrexate	0.658	0.397-1.090	0.1040
Prednisone	1.640	0.997-2.697	0.0512
Azathioprine	0.500	0.045-5.514	0.5714
Leflunomide	1.000	0.290-3.454	1.0000
Hydroxychloroquine	1.167	0.540-2.522	0.6952
Sulfasalazine	0.625	0.204-1.910	0.4097
Comorbidities			
Diabetes mellitus (90 days prior to index date)	3.308	1.779-6.151	0.0002
Chronic kidney disease (90 days prior to index date)	2.250	0.693-7.306	0.1772
Chronic obstructive pulmonary disorder (90 days prior to index date)	12.333	3.803-40.000	<.0001
Joint replacement (360 days prior to index date)	3.500	0.727-16.848	0.1182
Previous history of infection (hospitalized infection 12-months prior to cohort entry date)	8.500	1.964-36.790	0.0042
Prevalent or incident user of anti-TNF drug			
Prevalent (≥1 claim for exposed anti-TNF drug(s) between cohort entry date and 90-day exposure period)	0.781	0.463-1.318	0.3551
Incident (0 claims for exposed anti-TNF drug(s) between cohort entry date and 90-day exposure period)	1.280	0.759-2.160	0.3551

TABLE 3: Final multivariable logistic regression analysis of covariates with manual, backward, step-wise elimination to remove variables with a P-value >0.05

Variable	Multivariate Model Odds Ratio	95% Confidence Interval (CI)	Adjusted p-value
Other drug exposure 90 days prior to index date			
Prednisone	1.873	1.015-3.458	0.0447
Comorbidities			
Diabetes mellitus (90 days prior to index date)	2.963	1.445-6.078	0.0030
Chronic obstructive pulmonary disorder (90 days prior to index date)	9.233	2.755-30.947	0.0003
Previous history of infection (hospitalized infection 12 months prior to cohort entry date)	8.984	1.895-42.595	0.0057

FIGURES

FIGURE 1: Timeline of RA cohort



RA= rheumatoid arthritis
Anti-TNF = anti-tumor necrosis factor

FIGURE 2: Timeline of nested case-control study

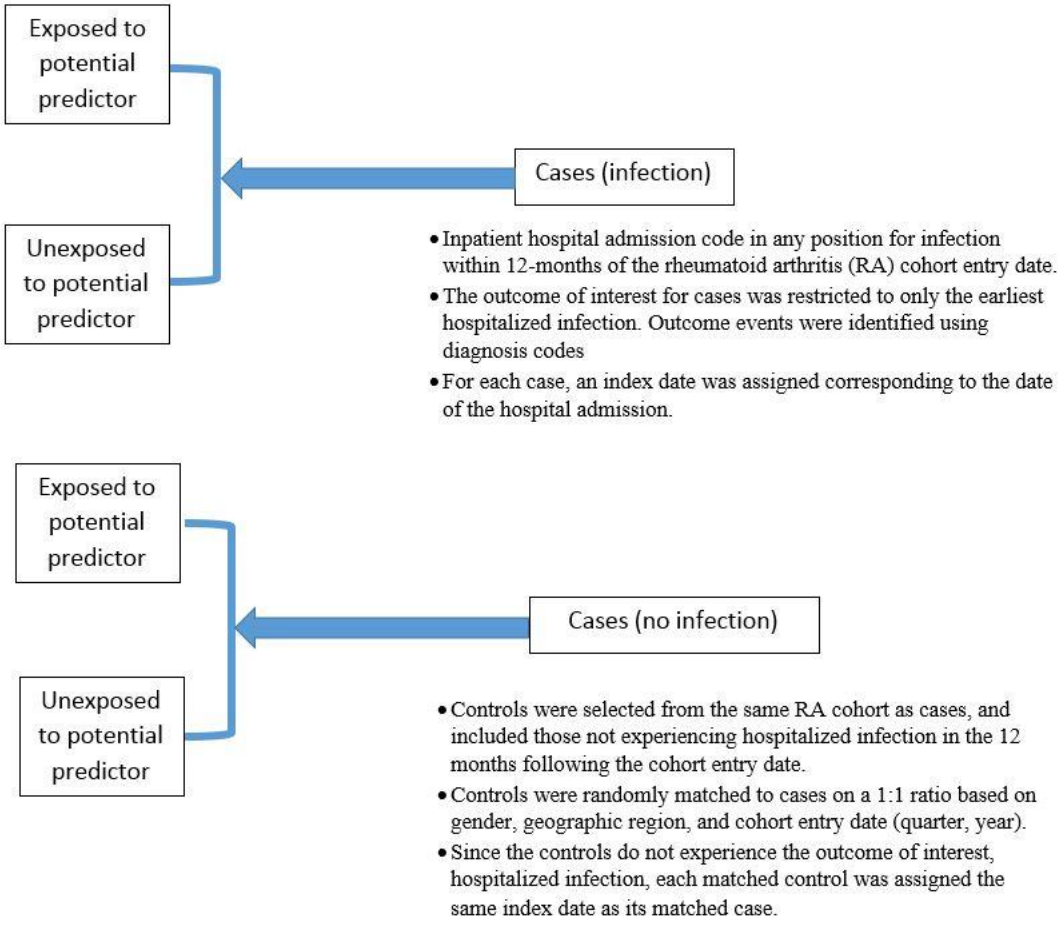
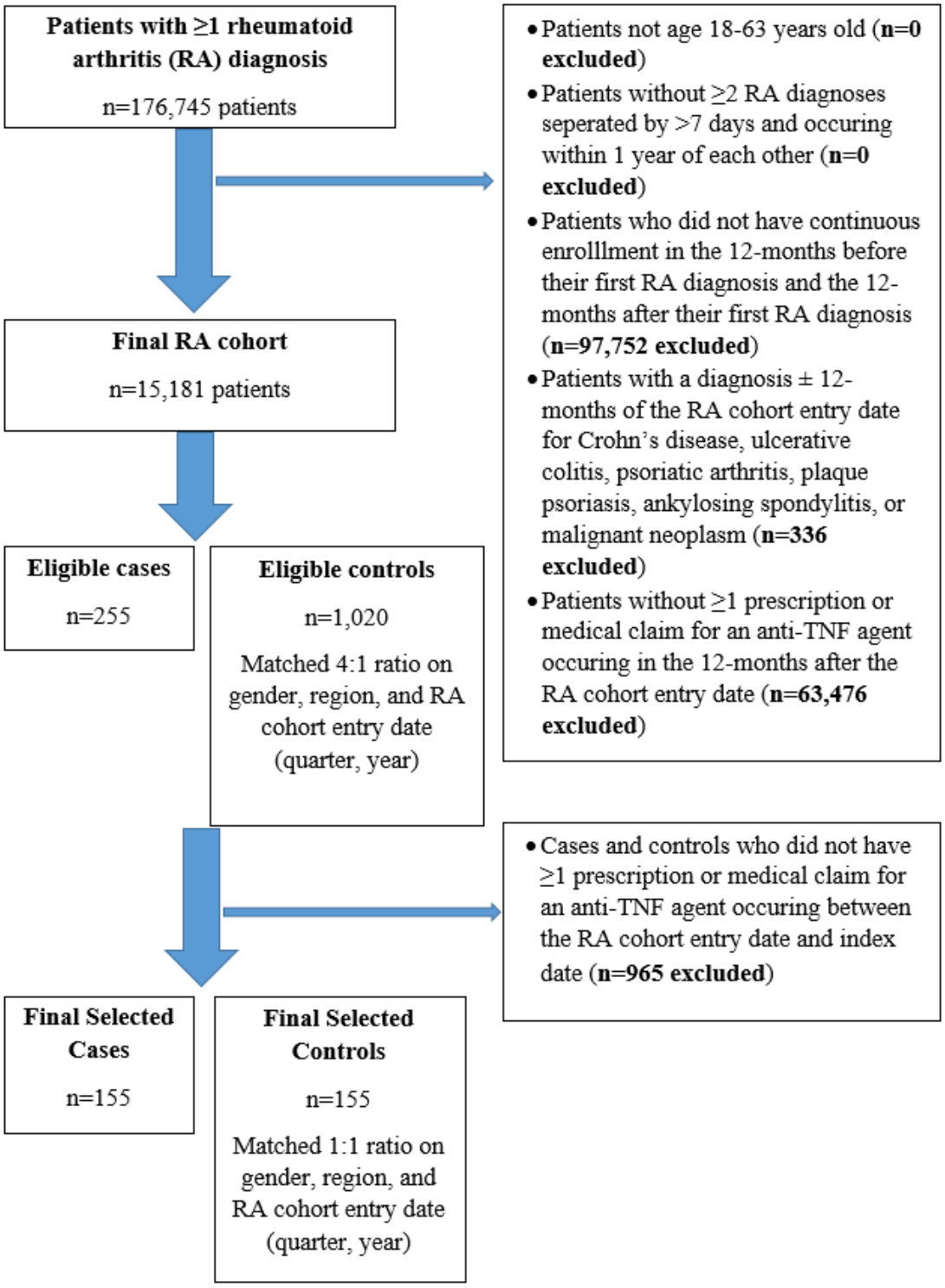


FIGURE 3: Study sample selection flowchart



RA = rheumatoid arthritis
Anti-TNF = anti-tumor necrosis factor

APPENDICES

APPENDIX 1: Literature review table

Author, Year	Design	Population	Inclusion/Exclusion Criteria	Exposure/Outcome Definition	Significant Predictors
Curtis et al[12], 2007	Retrospective cohort	▪ Medical and pharmacy administrative claims of large US health organization between May 1998 and December 2003	**Inclusion:** ▪ ≥18 years old ▪ ≥2 RA diagnoses ▪ Each individual had to have received an infusion or filled a prescription for an anti-TNF drug or filled at least 3 prescriptions for methotrexate	**Follow up:** ▪ Infections identified within 6 months of the most recent exposure to the anti-TNF or methotrexate **Exposure:** ▪ Patients who received an anti-TNF drug were the exposed cohort and those who received methotrexate only were the unexposed/comparator cohort ▪ Date of 1st exposure to the anti-TNF **Outcome:** ▪ Identified hospitalizations that occurred after index date with ≥2 ICD-9-CM codes for bacterial infections (at least 1 of these codes had to be based on a face-to-face encounter with a physician, additional ICD-9-CM codes could originate from a claim for a diagnostic test or procedure)	**Multivariate analysis:** ▪ Anti-TNF treatment (HR 1.94, 95% CI 1.32–2.83) ▪ Age (5-year increments) (HR 1.14, 95% CI 1.03–1.27) ▪ No. of face-to-face physician visits (HR 1.04, 95% CI 1.01–1.07) ▪ Prior infection (HR 1.46, 95% CI 0.85 2.51) ▪ Chronic obstructive pulmonary disease or asthma (HR 1.90, 95% CI 1.19–3.04) ▪ Diabetes mellitus (HR 1.75, 95% CI 1.10–2.78) ▪ Kidney disease (HR 3.23, 95% CI 1.35–7.73) ▪ Decubitus ulcer (HR 3.05, 95% CI 1.50–6.19) ▪ Mean prednisone dosage - ≤5 mg/day (HR 1.49, 95% CI 0.82–2.72 - 5–10 mg/day (HR 1.46, 95% CI 0.84–2.54) - ≥10 mg/day (HR 1.85, 95% CI 1.2–2.85)

Author, Year	Design	Population	Inclusion/Exclusion Criteria	Exposure/Outcome Definition	Significant Predictors
Favalli et al[21], 2009	Retrospective cohort	▪ Lombardy (Italy) Rheumatology Network (LORHEN) registry (since 1999)	**Inclusion:** ▪ ≥1 diagnosis of RA and ≥ 18 years old ▪ ≥1 infusion or filled a prescription for etanercept, infliximab, or adalimumab ▪ All patients treated in accordance with the Italian Society of Rheumatology guidelines for the use of anti-TNFα agents: Failure to respond to ≥1 course of combination therapy with full-dose traditional DMARDs, one of which is methotrexate unless contraindicated and disease Activity Score on 28 joints (DAS28) of >3.5 **Exclusion:** ▪ Active infection and/or history of malignancy or a pre-malignant condition, class III/IV congestive heart failure, or demyelinating disorders	**Follow up:** ▪ Followed for 1st administered anti-TNF agent until 36 months or first infection outcome **Exposure:** ▪ 1st administered dose of adalimumab, etanercept, or infliximab **Outcome:** ▪ Physician documented infection episodes recorded in medical charts or outpatient visits	**Multivariate analysis:** ▪ Age (per 1 year) (HR 1.03/year, CI 1.01–1.06) ▪ Prednisone daily dose > 5 mg (HR 2.89, 95% CI 1.12–7.48) ▪ Erythrocyte sedimentation rate (ESR) (HR 1.02 per every mm/h increase, 95% CI 1.00–1.03)

Author, Year	Design	Population	Inclusion/Exclusion Criteria	Exposure/Outcome Definition	Significant Predictors
Atzeni et al[22], 2012	Retrospective cohort	▪ GISEA (Italy) registry (since 2008)	**Inclusion:** ▪ ≥18 years ▪ RA diagnosis by rheumatologist ▪ ≥1 infusion or filled a prescription for etanercept, infliximab, or adalimumab ▪ All patients treated ≥6 months with anti-TNF agent or had discontinued anti-TNF earlier due to infection ▪ All patients treated in accordance with the Italian Society of Rheumatology guidelines for the use of anti-TNF agents: - Failure to respond to at least one course of combination therapy with full-dose traditional DMARDs, one of which is methotrexate unless contraindicated - Disease Activity Score on 28 joints (DAS28) of >3.5	**Follow up:** ▪ Followed for 1st administered anti-TNF agent until first infection outcome **Exposure:** ▪ 1st infusion of infliximab or filled prescription for adalimumab or etanercept ▪ If patients switched to 2nd anti-TNF agent, only time and adverse events of 1st agent used in analysis **Outcome:** ▪ Physician documented infection episodes, occurrence of adverse events captured every 6 months	**Multivariate analysis:** ▪ Corticosteroid therapy (OR 1.633, 95% CI 1.01-2.644) ▪ Concomitant DMARD during anti-TNF treatment (OR 2.14, 95% CI 1.28-3.595) ▪ Age at start of anti-TNF treatment (OR 1.036, 95% CI 1.02-1.053) ▪ Use of infliximab (OR 4.916, 95% CI 2.71-8.906) or adalimumab (OR 2.22, 95% CI 1.12-4.42) rather than etanercept

Author, Year	Design	Population	Inclusion/Exclusion Criteria	Exposure/Outcome Definition	Significant Predictors
Widdifield et al[23], 2013	Nested case-control	▪ Ontario health administrative data ▪ April 1, 1992 to March 31, 2010 data analysis	**Inclusion:** ▪ ≥66 years ▪ ≥2 billing code diagnoses of RA >60 days apart, but within 5 years ▪ ≥1 prescription for an oral glucocorticoid, a DMARD, or a biologic agent	**Follow up:** ▪ Followed on date when all inclusion/exclusion criteria were met until outmigration, death, or the end of the study (March 31, 2010) **Exposure:** ▪ Oral glucocorticoid, DMARD, or biologic ≤365 days before index date **Outcome:** ▪ Cases: Emergency department visit or hospital admission with primary diagnosis of infection between the later of April 1, 1998, or cohort entry, and March 1, 2010 ▪ Controls: Cases matched on age (±5 years), sex, and date of cohort entry (±1 year) to 5 controls from the same RA cohort	**Multivariate analysis:** ▪ Rural (ref. urban) (OR 1.51, 95% CI 1.44–1.58) ▪ Comorbidities - Diabetes Mellitus (OR 0.97, 95% CI 0.93–1.01) - Chronic lung disease (OR 1.31, 95% CI 1.25–1.36) - Renal disease (OR 1.26, 95% CI 1.18-1.36) ▪ Current glucocorticoid use (mg/day) - ≤5 (OR 3.96, 95% CI 3.67–4.27) - ≥20 (OR 7.57, 95% CI 6.87–8.34) ▪ Current methotrexate use (mg/day) - ≤10 (OR 2.38, 95% CI 2.22–2.56) - >10 (OR 2.97, 95% CI 1.90–4.64) ▪ Current anti-TNF use (OR 1.60, 95% CI 1.19-2.15) ▪ Extra articular features of RA (OR 1.11, 95% CI 1.07–1.16) ▪ Joint replacements (OR 1.01, 95% CI 0.97–1.06) ▪ Previous infections (OR 1.51, 95% CI 1.45–1.57)

Author, Year	Design	Population	Inclusion/Exclusion Criteria	Exposure/Outcome Definition	Significant Predictors
van Dartel et al[24], 2013	Retrospective cohort	▪ Dutch Rheumatoid Arthritis Monitoring (DREAM) biologic registry (since 2003) ▪ Radboud University Nijmegen Medical Centre (RUNMC) (before 2003) ▪ 5-year data analysis	**Inclusion:** ▪ Using adalimumab, infliximab or etanercept as 1st anti-TNF agent **Exclusion:** ▪ Received anti-TNF agent as part of a clinical trial.	**Follow up:** ▪ Followed for 1st administered anti-TNF agent until 5 years of observation time or at the end of follow-up, or after stop of an anti-TNF agent plus five times the half-life, or after the occurrence of the 1st serious infection ▪ Patients who switched between anti-TNF agents, the treatment with the next anti-TNF contributed to the observation time if it started within five times the half-life of the former anti-TNF agent **Exposure:** ▪ 1st administered dose of adalimumab, etanercept, or infliximab **Outcome:** ▪ FDA definition for serious adverse event: hospitalization and/or intravenous antibiotic treatment, life threatening, disabling daily activities	**Multivariate analysis:** ▪ Age (ref. <55) - 55-65 (HR 1.07, 95% CI 0.66-1.74) - >65 (HR 2.11, 95% CI 1.39-3.22) ▪ Corticosteroid use baseline (HR 1.54, CI 1.08-2.20) ▪ Visual analogue scale (VAS) pain baseline (HR 0.98, CI 0.98-1.00) ▪ Health Assessment Questionnaire (HAQ) baseline (HR 1.57, CI 1.12-2.22) ▪ Tender joint count 28 joints (TJC28) (HR 1.04, CI 1.01-1.06) ▪ Presence of comorbidities (HR 1.31, CI 0.98-1.75)

Anti-TNF = anti-tumor necrosis factor
CI = confidence interval
DMARD = disease modifying anti-rheumatic drug
HR = hazard ratio
OR = odds ratio
RA = rheumatoid arthritis

APPENDIX 2: ICD-9-CM codes to identify exclusion criteria diagnoses[25,26]

Diagnosis	**ICD-9-CM Code**
Crohn's disease	555.0 555.1 555.2 555.9
Ulcerative colitis	556.0 556.1 556.2 556.3 556.4 556.5 556.6 556.8 556.9
Psoriatic arthritis	696.0
Plaque psoriasis	696.1
Ankylosing spondylitis	720.0
Malignant neoplasm	140.x 172.x 173.00, 173.09 173.10, 173.19 173.20 173.29 173.30 173.39 173.40 173.49 173.50 173.59 173.60 173.69 173.70 173.79 173.80 173.89 173.90 173.99 174.x 209.36 209.7x

APPENDIX 3: ICD-9-CM codes to identify hospitalized infection[27]

Diagnosis	**ICD-9-CM Code**
Meningitis	003.21 036.0 049.0 091.81 094.2 098.82 320.xx
Encephalitis	036.1 323.x 094.81 130
Cellulitis	040.0 569.61 681.xx 682.x 785.4 035 608.4 681.xx 614.3 528.3 566 597.0
Endocarditis	036.42 093.2x 98.84 391.1 397.9 421.x 421.9 422.92
Pneumonia	003.22 481.0 482.xx 483.x 485.x 486.x 513.0
Pyelonephritis/urinary tract infection	590.xx 599.0
Septic arthritis	003.23 056.71 711.9x 711.0x 098.5x
Osteomyelitis	003.24 730.2x 526.4 730.2x 526.4 730.0x 730.1x 376.03
Bacteremia/septicemia	038.xx 041.xx 790.7
Upper respiratory tract infection	34 381.5x 382.x 383.0x 383.1 383.9 461.x 462.x 463 465.x 466 464.0x 472.x 473.x 475 510 510.9
Abdominal abscess	95.2 540.1 569.5 567.x 572 590.2 601.2 614.4 998.59
Brain abscess	324.x
Cholecystitis	574.x 575 576.1 575.1x 575.1 575.12 575.11
Prostate infections	98.32 98.12 131.03 601.x
Gastroenteritis	001 002 003 003.0 004 005 008 008.1 008.2 008.4 008.5 009.x
Infectious conjunctivitis	372.0x 77.9 32.81
Device-associated infections	996.6x
Local infections of skin and subcutaneous tissue	686.1 686.8 686.9
Gangrene	785.4
Retropharyngeal abscess	478.21 478.24 478.22

APPENDIX 3 (continued): ICD-9-CM codes to identify hospitalized infection[27]

Diagnosis	**ICD-9-CM Code**
Breast abscess	611.0
Splenic abscess	289.59
Pyogenic granuloma	686.1
Post-traumatic wound infection	958.3
Postoperative wound infection	998.5
Infective myositis	40.81
Necrotizing fasciitis	728.86

APPENDIX 4: National drug codes (NDC) and Healthcare Common Procedure Coding System (HCPCS) codes to identify pharmacy or medical claims for the self-injectable drugs adalimumab and etanercept

Proprietary (Non-Proprietary) Name	**11 Digit National Drug Code (NDC)**	**Healthcare Common Procedure Coding System (HCPCS)**
Humira (adalimumab)	00074006702 00074024302 00074024371 00074055401 00074055402 00074055404 00074055406 00074055471 00074055473 00074055474 00074254001 00074254003 00074379701 00074379902 00074379903 00074379906 00074379971 00074433901 00074433902 00074433906 00074433907 00074433971 00074433973 00074433974 00074634702 00074937402 00074937471	J0135
Enbrel (etanercept)	58406042534 58406043504 58406044504 58406045504	J1438

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